The Journal of Allergy

VOL. 17 NOVEMBER, 1946 No. 6

American Academy of Allergy

Second Annual Meeting, Chicago, Ill., Dec. 10 and 11, 1945

(Continued)

STUDIES IN FOOD ALLERGY*†

V. ANTIGENIC RELATIONSHIP AMONG MEMBERS OF FISH FAMILY

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MULTIPLE sensitivity to members of the fish family has been a common clinical observation. In a previous communication,[1] the authors presented immunologic evidence of the existence of a common antigenic factor among the members of the Mollusca and Crustacea families. It was further demonstrated that the Crustacean antigen was not related to the Molluscum antigen and that neither of them bore any relationship to members of the true fish family. The zoologic classification for the fish family previously presented is herewith reproduced (Table I). The purpose of these studies was to investigate the existence and relationship of the various types of antigens existing in the true fish family.

PROCEDURE

One species was chosen as a representative of each of the fish families. Those selected are underlined in the classification table. Direct skin tests by the intracutaneous method were performed on six fish-sensitive patients with all the available fish extracts. Considerable caution had to be exercised in skin testing, since such patients would develop violent constitutional symptoms if too many extracts were tested at the same time. The adopted routine consisted in testing such patients with only one fish extract per visit. All extracts used for direct skin testing were diluted so that they contained 0.1 mg. total nitrogen per c.c. The sera of these patients were then obtained for passive transfer experiments. Passively transferred sites were first tested with all the available fish extracts. Concentrated extracts were used in all passive transfer experiments so as to eliminate the quantitative factor in evaluating the end results of neutralization. After neutralization of a site had been completed by exhaustion of the specific

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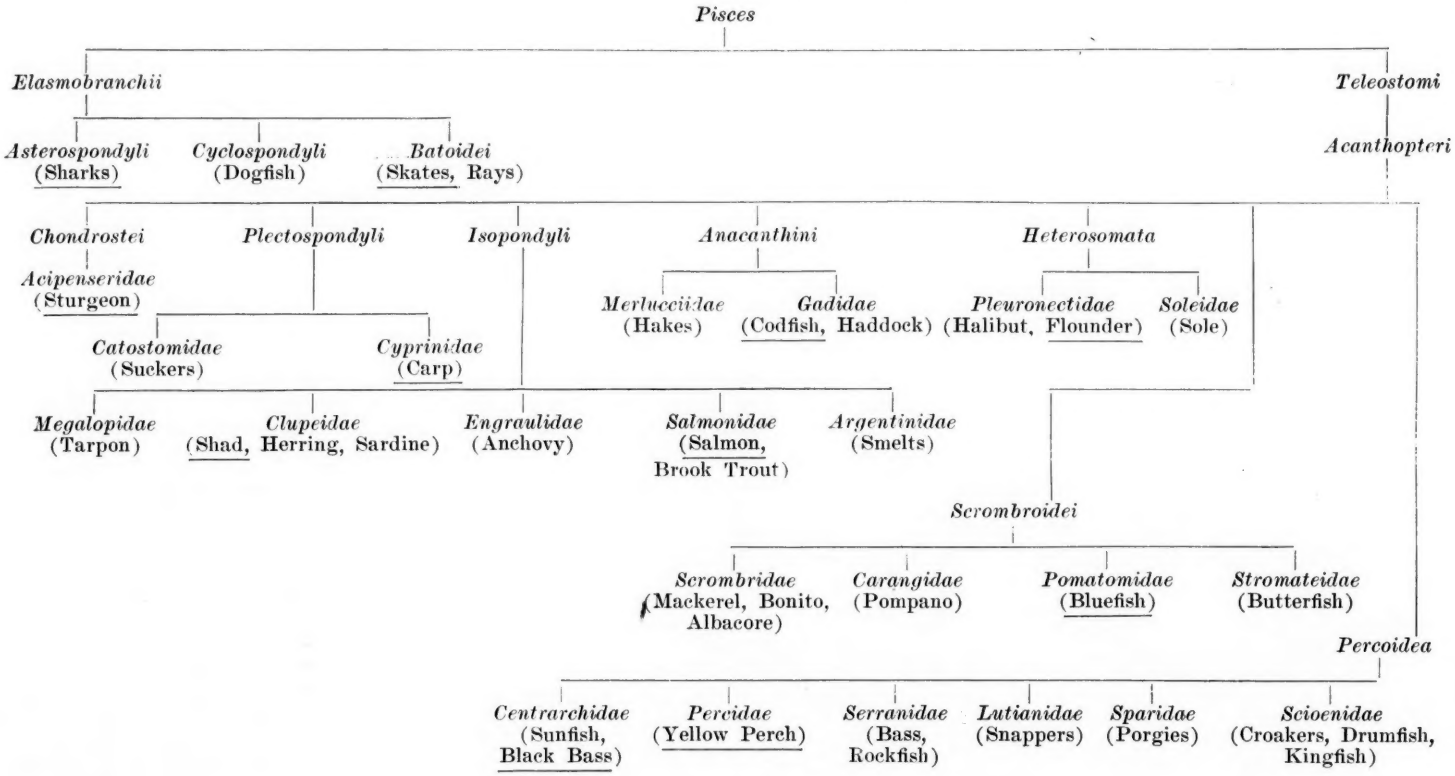
†Read before the Second Annual Meeting of the American Academy of Allergy, Chicago, Ill., December 11, 1945.

TABLE I. CLASSIFICATION OF FISHES (BREDER)



antibody, it was tested successively with all other members of the fish family. For example, after the site had been exhausted with cod and a negative reaction obtained, it was successively reinjected, after forty-eight-hour intervals, with other fish extracts such as flounder, shad, carp, etc.

The same procedure was adopted for each fish extract studied. Care was taken to ascertain that the skin sites used had not been rendered refractory by repeated testing with concentrated extracts. This was accomplished by testing each site at the completion of the study with a totally unrelated antigen to which the patient was known to be sensitive (ragweed).

The same procedure was then repeated, except that initial neutralization of the serum in vitro was used instead of neutralization by direct exhaustion of the passively transferred sites. This was accomplished by the admixture in a test tube of serum and concentrated antigen in a ratio of 2:1. The mixture then was kept at room temperature for one hour and placed in a refrigerator overnight. Passive transfer sites were prepared with this material the following day. In order to make certain that neutralization was complete, each site was tested with the extract used for neutralization of the antibody. A negative reaction indicated complete neutralization. The sites were then tested with various other fish extracts and at the end with a totally unrelated allergen, as previously described.

A study was then made of the antigenic relationship between fish roes and their parent substances. Sturgeon and its roe (caviar) and shad and shad roe were employed for that purpose. Neutralization in vitro and by exhaustion were carried out in a manner similar to that already described.

Clinical experiments were conducted on all available patients in an attempt to corroborate the experimental findings. This included the ingestion of related and unrelated fish, the feeding of fish that had never been eaten by the patient, and the exposure of the patient to odors from both the raw and cooked fish.

RESULTS

A fish-sensitive patient reacting to one member of the family was found invariably to give positive skin reactions to all members of the entire order. These skin reactions were found to vary in intensity. Thus, patients showed doubtful or slight reactions to some members but gave marked reactions to other fish, even though routine test-strengths were used. In such instances, testing with the next higher concentration invariably provided stronger reactions. It, likewise, was noted that these patients always gave positive skin reactions to many fish that they never ate, including many inedible ones like shark and skates. These skin-test findings were corroborated by similar findings in the direct passive transfer experiments, demonstrating the presence of specific homologous antibodies in the circulating blood of these patients.

The results of the neutralization studies, as indicated equally well either in vivo or in vitro, showed several interesting points. Thus, a distinct difference was observed between the members of the edible and inedible groups. Those belonging to the edible group (subclass *Teleostomi*) could neutralize the antigen in the inedible group (subclass *Elasmobranchii*). However, the antigen in the

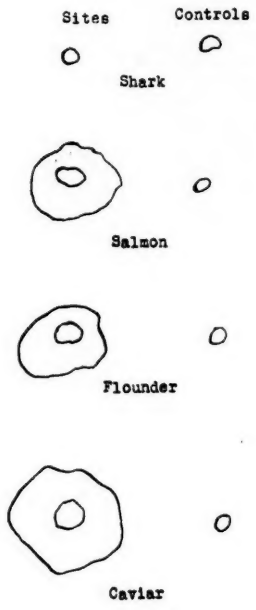


Fig. 1.—Type of reactions obtained after neutralization in vitro with shark extract.

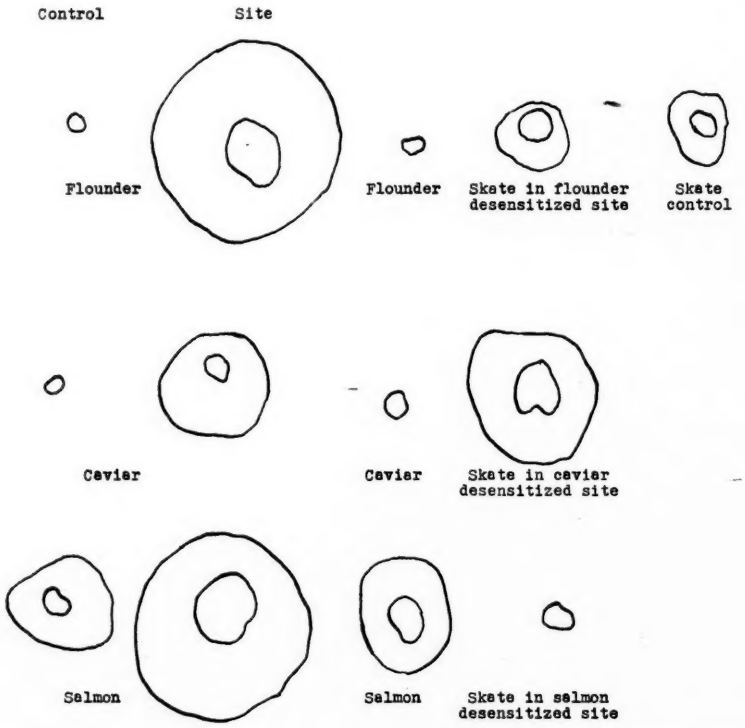


Fig. 2.—Types of reactions obtained with skate after neutralization with various fish extracts.

inedible group did not neutralize that of the edible. Thus, for example, the shark or skate antibody could be neutralized by other edible fish extracts such as flounder, salmon, caviar. The salmon, caviar, or flounder antibody, on the other hand, was only partially neutralized by the shark and skate antigens. These results are illustrated in Figs. 1 and 2.

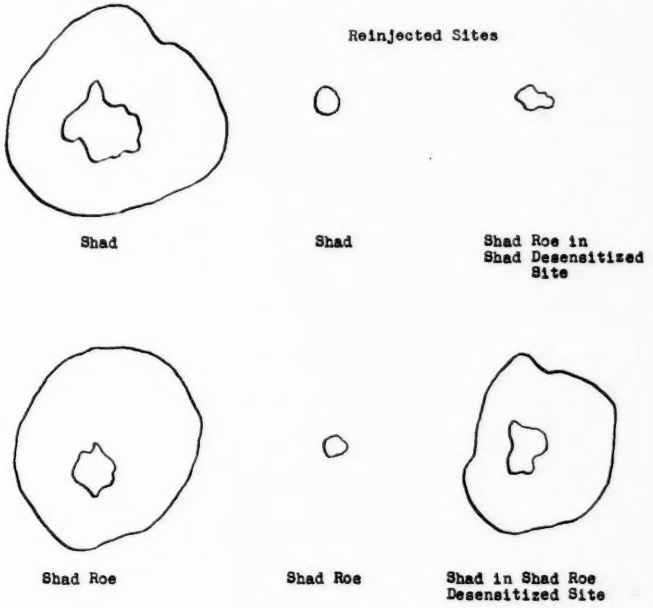


Fig. 3.—Relationship between shad and shad roe.

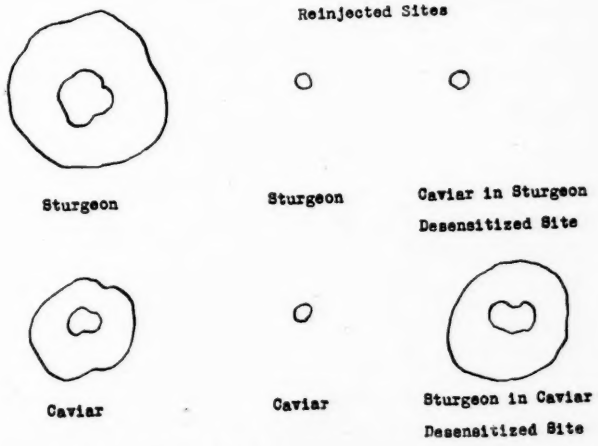


Fig. 4.—Relationship between sturgeon and caviar.

The antibody of the fish roe was neutralized by its parent substance, but the roe antigen was incapable of neutralizing the parent antibody. This relationship was shown both for shad and shad roe, and for sturgeon and caviar, as shown in Figs. 3 and 4.

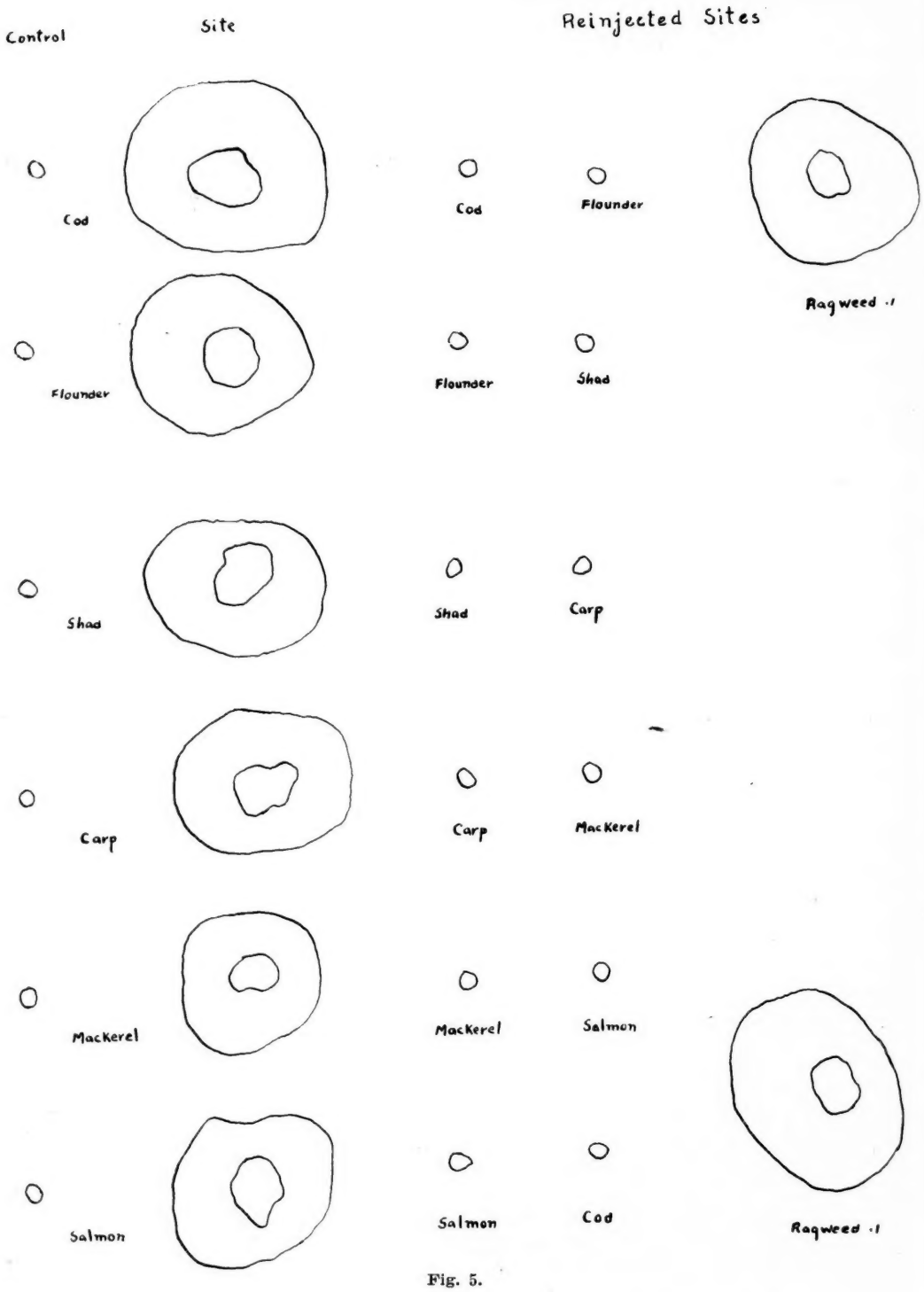

Control
Site
Reinjected Sites
Cod
Cod
Flounder
Ragweed .1
Flounder
Flounder
Shad
Shad
Shad
Carp
Carp
Carp
Mackerel
Mackerel
Mackerel
Salmon
Salmon
Salmon
Cod
Ragweed .1

Fig. 5.

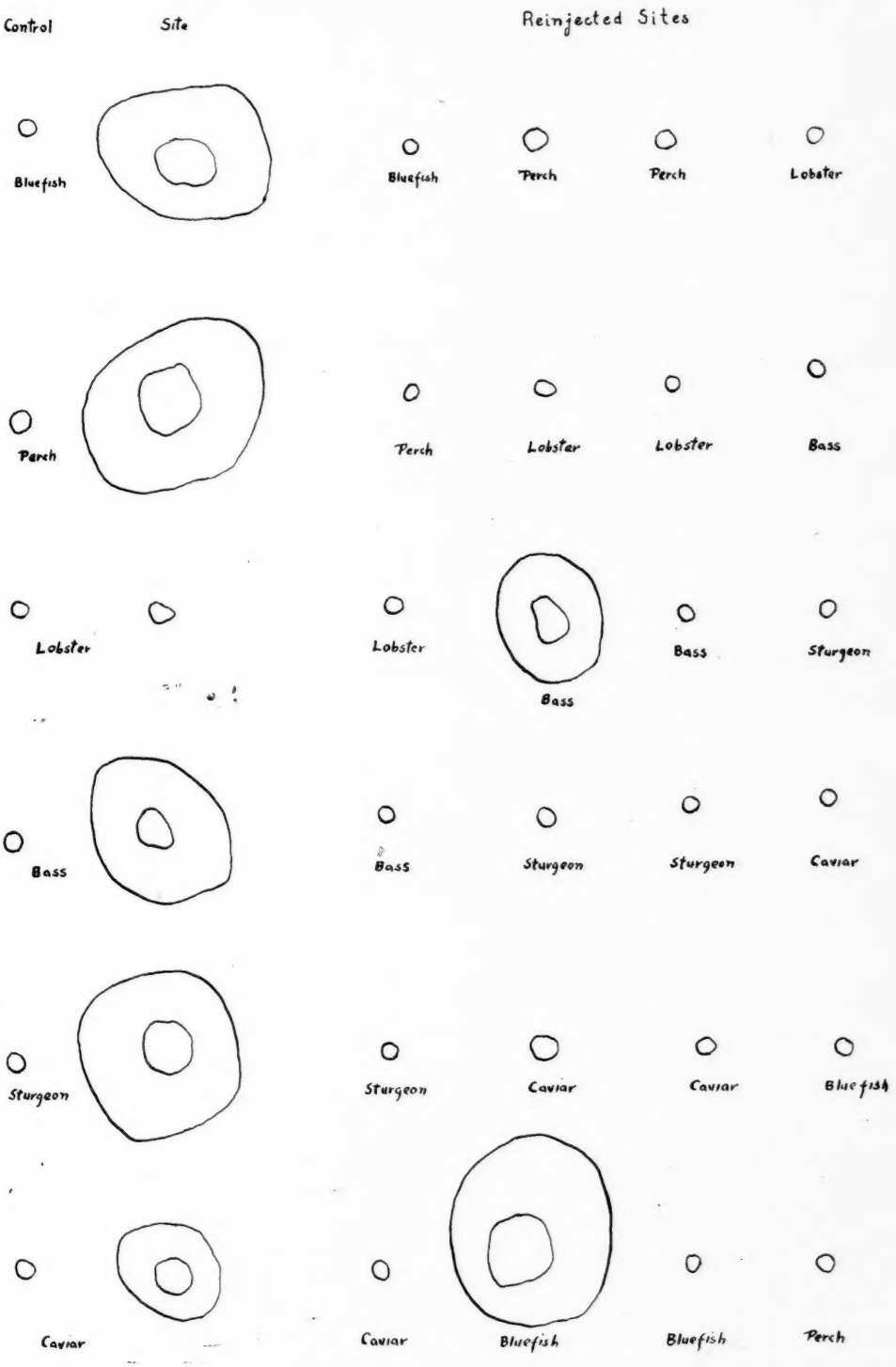

Control Site
Reinjected Sites
Bluefish
Bluefish
Perch
Perch
Lobster
Perch
Perch
Lobster
Lobster
Bass
Lobster
Lobster
Bass
Bass
Sturgeon
Bass
Bass
Sturgeon
Sturgeon
Caviar
Sturgeon
Sturgeon
Caviar
Caviar
Bluefish
Caviar
Caviar
Bluefish
Bluefish
Perch

Fig. 6.

The neutralization of the passively transferred site by one of the edible fish extracts obliterated reactions to all other members of this class. The manner in which this was accomplished is illustrated in Figs. 5 and 6. It is to be noted that, after completion of all the neutralizations, a positive reaction was still elicited with ragweed extract; also that a negative test was obtained with lobster extract, indicating an absence of sensitivity to the Crustacea; finally, bluefish antigen still gave a positive reaction in the caviar desensitized site, indicating that the former contained an antigen not present in caviar.

Clinical observations were more difficult to obtain because of the many untoward reactions which follow and the reluctance of the patients to cooperate in any procedure that might deliberately precipitate symptoms. All patients exhibiting reactions to the fish family and not to the Mollusca or Crustacea were able to eat unlimited quantities of shellfish with impunity. Several patients developed urticaria and asthma following the ingestion of fish which they had never eaten before. Thus, one child who had never tasted caviar manifested urticaria following her initial contact with this substance. Another fish-sensitive child who never ate salmon or tuna fish, but gave positive skin reactions to these fish, developed swelling of the lips and mouth immediately following the initial contact with these substances. This corresponded to similar clinical experiences with the members of the Mollusca or Crustacea group, for patients sensitive to one member of these groups were found to be skin and clinically sensitive to other members, even though they never had eaten them previously.

Three fish-sensitive patients exposed to the odors of uncooked fish emanating from a large fish market began to develop urticaria and asthma within a relatively short time. The earliest reaction occurred in five minutes in one of the more sensitive individuals, but at the end of thirty minutes all three had either subjective or objective symptoms, or both. These three individuals were kept in the hospital kitchen on a day when fish was being cooked and when the odors emanating therefrom were rather heavy. The reactions in this instance were more immediate than before, the first clinical symptoms appearing in one in four minutes and appearing in all at the end of fifteen minutes. No attempts were made to obtain this volatile substance in solution for skin testing purposes.

DISCUSSION

It is evident from these experiments that a common antigen exists among the various members of the true fish family. That the antigen is multiple or complex rather than single is indicated by the fact that edible fish extracts contained an antigen not present in the inedible group. Furthermore, the roes of various fish do not contain all the antigens present in their mother substance. In this respect their relationship resembles that previously noted between horse serum and horse dander, and also among the shellfish. The distribution of these antigens in the edible and inedible groups closely parallels the divisions in the zoologic classification. The presence of a common antigen among such a widespread group serves to explain the existence of positive skin reactions to fish

which the patient had never ingested previously. This, likewise, was substantiated by our clinical results in the limited group at our disposal.

The quantitative difference in reactions to the various extracts, whether used in direct skin tests or for passive transfer, indicates that, while all the members of the fish family contain a common antigen, it is present in varying amounts in the different extracts. This may be due either to the method of preparation or to an actual quantitative difference in the antigenic content present in the fish itself. This could be determined more definitely if it were possible to isolate the active principle by better methods of concentration and purification.

From a practical clinical standpoint these findings serve to explain the variation in the degree of skin reactions obtained by testing fish-sensitive patients with other members of the true fish family. The demonstration of the existence of a common antigen also corroborates the long-standing belief that fish-sensitive patients often are clinically sensitive to all fish, including the roes. The fish antigen is a powerful urticariogenic and asthmogenic substance capable of producing severe reactions within a few minutes after ingestion. Allergists long have realized the necessity for caution in testing individuals with a clinical history of fish sensitivity, being careful to use more dilute concentrations than that used routinely, and to test with only one extract at a time. Since there is a common antigen among fish, the question quite naturally arises as to the advisability of employing only a single member of the entire edible fish family in testing. This would seem inadvisable, however, in view of the quantitative variation which was found to exist among the individual members tested, although some reduction in the number of extracts used certainly could be made without detriment—thus, if a patient gave a marked reaction to the first fish tested, it would be unnecessary to test all the other fish since, in such a case, all fish would be automatically excluded from the diet. On the other hand, if negative or only slight reactions are obtained, then other fish extracts should be used to see if this sensitivity can be corroborated. A similar procedure should be adopted for the shellfish.

It is to be remembered, of course, that these experiments were performed upon patients who were markedly sensitive to fish and who, therefore, are more likely to be allergic to all the members of the fish family. Statements are to be found in various publications and in textbooks indicating that patients have noted that certain fish cause symptoms upon ingestion, whereas others could be eaten with impunity. Furthermore, it has been observed that specific positive skin reactions are obtained with some fish, whereas other fish extracts give negative reactions. As already indicated, the existence of a quantitative variation in the amount of antigen present may explain these apparent discrepancies—thus patients with negative skin reactions may give positive reactions upon routine testing if the next higher concentration is used. Furthermore, clinical symptoms were absent in one of the patients studied when a little seafood was ingested, but could be brought on by the ingestion of a larger amount. Clinical reports as to the existence of sensitivity to only one or a few fish and not to others should be checked carefully by adequate clinical trial before such conclu-

sions are drawn. If such a situation is found to exist, it still does not invalidate the demonstration of the existence of a common antigen. The same situation, no doubt, exists here as was found true, for example, of horse dander and horse serum. Patients markedly sensitive to horse dander are also usually sensitive to horse serum. However, positive reactions may be obtained to horse dander alone without any reaction to horse serum or vice versa. Much depends in such instances upon the particular antigenic fraction involved and the degree of sensitivity, both factors determining the patient's clinical and skin test reactions.

The results of these experiments also are valuable in helping to explain the existence of positive skin and clinical reactions to substances which the patient never has eaten. One of the criticisms directed against all skin tests has been the finding of positive reactions to substances which the patient never eats or is in contact with. Most of these can now be readily explained upon the basis of the presence of a common antigenic factor as has been shown to exist among the true fish, the shellfish, or similar food groups; also among inhalants like cottonseed and kapok, pollens, and various Mammalian sera.

Finally, the demonstration that fish odors produced during cooking precipitated urticaria and asthma in the three patients tested verifies the clinical reports of similar experiences by other observers. It suggests that the fish antigen contains a volatile fraction, the exact nature of which can be determined only by further investigation.

SUMMARY

1. A common antigen was shown to be present among the members of the true fish family. This antigen apparently possesses more than one fraction, since one fraction present among the edible fish was absent in the inedible ones; also, a fraction was absent in fish roe that could be found in its parent substance. The distribution of these antigens among the various species closely parallels the zoologic classification.

2. A quantitative variation in antigenic content either as judged by direct skin testing or passive transfer existed among the various species. This warrants continued use of multiple fish extracts in routine skin tests. However, where clinical history indicates the presence of exquisite sensitiveness, a marked positive reaction to one member should be taken as representative of the entire group. The necessity for caution in testing for fish sensitivity is emphasized.

3. The demonstration of a common antigenic factor explains the skin and clinical reactions manifested by patients to fish they had never eaten. This is helpful in the clinical interpretation of skin test reactions in general.

4. Finally, proof is offered of the ability of fish odors to induce clinical symptoms in sensitive patients.

DISCUSSION

DR. MATTHEW WALZER, Brooklyn.—The authors are to be congratulated on the thoroughness of their investigation. It was gratifying to see them check the results of their in vivo neutralization experiments by studies with the in vitro neutralization technique. So many of the erroneous conclusions which have appeared in the literature on the subject of antigenic

relationships have resulted from a failure to appreciate the pronounced limitations of the in vivo neutralization technique.

We have, in our own experience, encountered evidence to support the authors' concept of common antigens among the edible and inedible groups of fish. K. Bowman and Parfentjev, who were investigating the antigenicity of shark pepsin, found that it induced marked reactions on a site passively sensitized with a human serum containing reagins for flounder and other edible fish.

These studies by Tuft and Blumstein again demonstrate the pronounced tendency manifested by atopic patients to produce reagins excessively for particular types of antigens even though the exposures to them have been slight and occasional. This characteristic has already been well illustrated in relation to pollen allergens in an intensive study by Harten and Bowman on a large series of hay fever patients. The development of reagins to many related allergens in a particular group is more likely to be the result of many exposures to similar allergens rather than of a single contact with one allergen.

REFERENCE

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MEASUREMENT OF CIRCULATING RAGWEED ANTIBODIES AND ANTIGEN

Correlation with Symptoms and Treatment*†‡

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THE purpose of this investigation was to study and correlate seasonal circulating ragweed antigen, which was described in a previous communication,[1] with thermostable antibody and the relation of each of these to reagin titer, symptoms, pollen count, and treatment with pollen extract.

During this study, blood samples were obtained from both treated and untreated ragweed-sensitive patients and from normal, untreated individuals. No set schedule of treatment in respect to dosage or interval between injections was adopted. The patients studied received either the perennial or annual type of treatment, and varied from those extremely sensitive to those relatively insensitive.

Considerable care was taken in the evalution of symptoms and, in spite of detailed records, it was realized that appraisal of symptoms is always subjective on the part of both the clinician and the patient. Individual variations in exposure to pollen modify the improvement produced by specific pollen therapy. However, an evaluation of symptoms was attempted by reviewing each week a daily memorandum kept by the patient. A symptom score system was then adopted whereby symptoms for each week were classified as 0, 1, 2, 3, and 4 in ratio to severity, and these were added as an accumulative score for the season for each patient (Table II).

Blood samples were drawn at four-week intervals from March until August 15, after which the interval was shortened to one week. The samples were always obtained during each clinic visit prior to injection with pollen extract. Whole ragweed extract was used for therapeutic injections.

Circulating antigen, thermostable antibody, and reagin were determined on each blood within twenty-four hours after it was received. This entailed the setting up and titration of several hundred tubes each week. For this reason, the number of patients studied was limited to 29 treated cases and 11 controls.

METHODS

Determination of Circulating Antigen.—Freshly centrifuged human serum was added to precipitate-free, standardized anti-ragweed rabbit serum in equal volumes (0.25 ml.) and the resultant precipitate appearing after incubation,

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†Presented, in part, before the Second Annual Meeting of the American Academy of Allergy, Chicago, Dec. 11, 1945.

‡This investigation was supported by a grant from the John and Mary R. Markle Foundation.

refrigeration, and centrifugation was measured in Meloche capillary tubes according to the method previously described.[1]

Control tests were run simultaneously with anti-timothy rabbit serum. The few human sera which showed precipitate in the controls were discarded from the study. Preseasonal sera and late postseasonal sera of each patient were also tested for circulating antigen, and none was found.

Determination of Thermostable Antibody.—The precipitin reaction was used to measure thermostable antibody.[2] Samples of human sera were heated for one hour at 60° C. and allowed to cool. Reagins were thereby destroyed. Ragweed extract in serial dilutions was measured directly into Meloche capillary tubes. An equal volume (0.13 ml.) of freshly centrifuged, undiluted, heated human serum was then added. The mixture was shaken in an automatic shaker for two minutes, and placed in the refrigerator for eighteen hours.

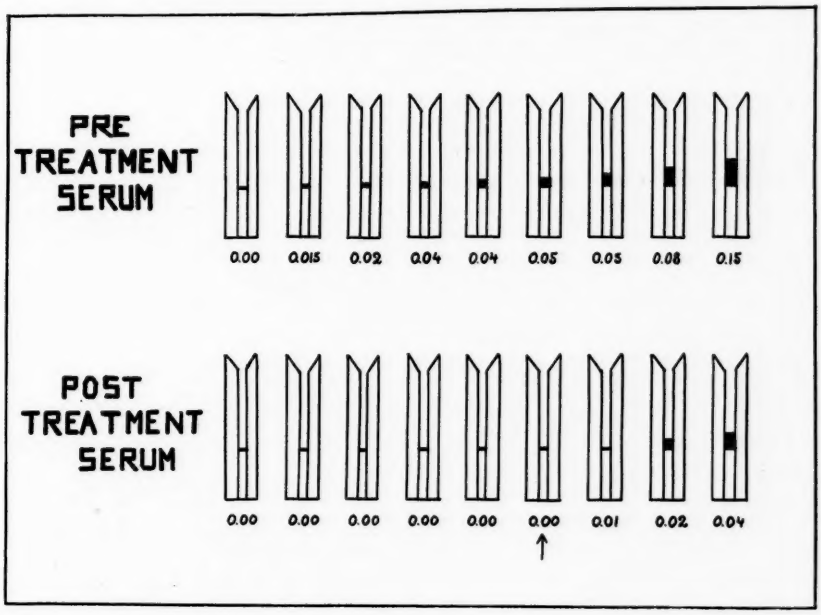


Fig. 1.—Schematic representation of quantitative precipitin reaction for measurement of thermostable antibody. Figures equal amount of precipitate in cubic millimeters.

Then 0.25 ml. of precipitate-free, standardized anti-ragweed rabbit serum was added to each mixture. The tubes were placed in a water bath at 37° C. for one hour and then in a refrigerator overnight. They were then centrifuged and the volume of precipitate measured. In all instances, freshly melted and diluted anti-ragweed rabbit serum from a frozen stock, and diluted cryochemed low ragweed extract were used. Both the antigen and ragweed antiserum were assayed at frequent intervals.

The tube in the series next to the one in which a precipitate appeared represented the end point in which reagin-free human serum interfered with the action of precipitins in the rabbit serum for ragweed antigen. Values were

expressed as units of protein nitrogen of the ragweed antigen in the mixture (Fig. 1). There are limitations to the precipitin method in that neutralization of less than 100 units cannot be detected easily. However, its advantage is that end points are sharp and may be measured very accurately.

Determination of Reagin.—The amount of skin sensitizing antibody was titrated by the serum dilution method. Serial dilutions of unheated human serum from ragweed-sensitive patients were made. Then 0.05 ml. of each dilution, freshly prepared, was injected intracutaneously on the backs of normal, nonsensitive individuals. Because of variations in the receptiveness of the skin to passive sensitization, several recipients were used for the titration of each serum. The sera were tested at the time each blood was obtained, and again when a series of sera could be tested on the same subject simultaneously for comparison. The first dilution of injected serum which, when tested forty-eight hours later with 0.02 ml. of 500 units of ragweed extract, elicited a definitely positive reaction was considered the endpoint. This was likewise expressed as the number of protein nitrogen units with which reagin first reacted.

DISCUSSION

Thermostable Antibody.—One of the advantages of the precipitin method is that with satisfactory stock of desiccated antigen and stock frozen rabbit antiserum always available, thermostable antibody can be determined as the bloods are drawn. We were also able to observe fluctuations in thermostable antibody in sera taken at frequent intervals during the entire course of the experiment, and curves of successive values for each patient were plotted. This is in contrast to the method of titrating mixtures on normal skin by passive transfer which frequently requires all comparable sera be tested simultaneously, and the difficulties and limitations in the use of human recipients are considerable. This is particularly true when the passive transfer test is employed with serial dilutions for the measurement of comparative tests.

It was found that thermostable antibody was induced as a result of specific antigen therapy, but there is no uniform relationship between titer of thermo-

TABLE I. COMPARISON BETWEEN THERMOSTABLE ANTIBODY IN RAGWEED SENSITIVE PATIENTS TREATED WITH RAGWEED ANTIGEN AND TOTAL TREATMENT DOSAGE

THERMOSTABLE ANTIBODY TITER	TOTAL DOSAGE RAGWEED ANTIGEN
	(protein nitrogen units)
10,000	64,000
8,000	78,000
8,000	3,080
7,000	37,395
7,000	15,950
6,000	24,963
6,000	4,710
5,000	47,500
5,000	10,200
3,000	33,080
3,000	4,179
2,000	21,540
2,000	131
1,000	957
1,000	69

stable antibody and total dosage as given in the traditional perennial and annual methods of treatment. (Table I.) Although in some patients the thermostable antibody response was in ratio to the amount of treatment received (Fig. 2), this was by no means consistently true (Fig. 3). The response was individual, regardless of whether this was the initial year of specific therapy, or whether the patient had received treatment for many years. Loveless[3] and Gelfand and Frank[4] have likewise observed that such response differs from individual to individual.

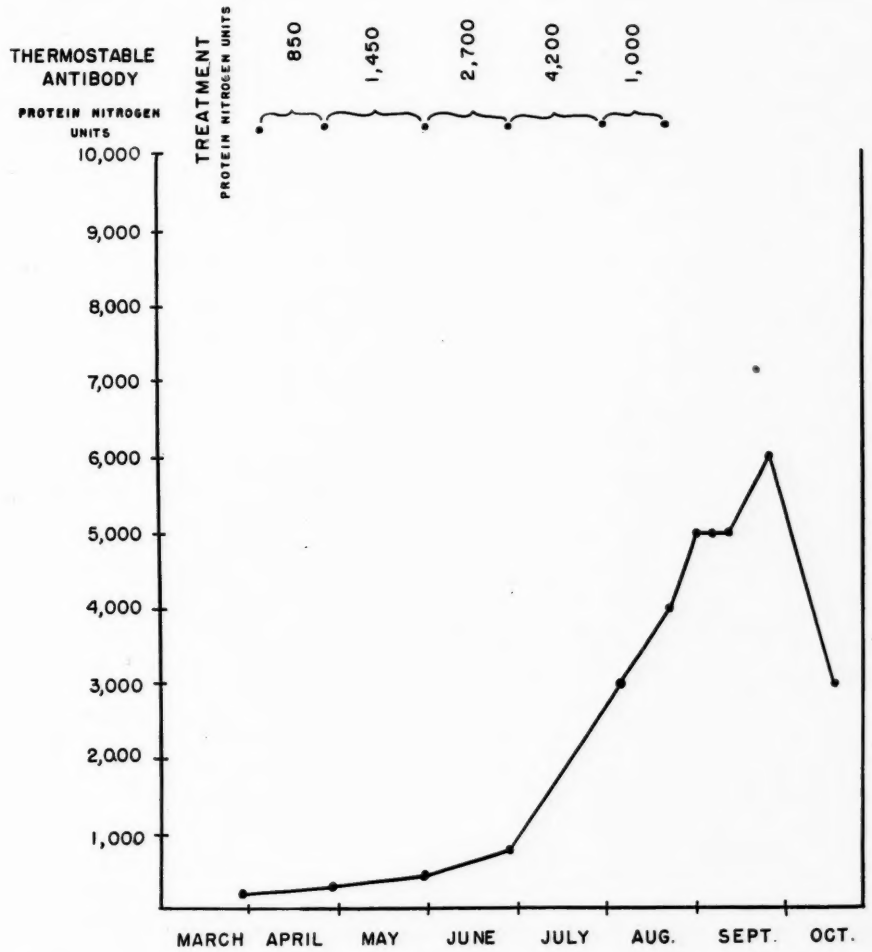


Fig. 2.—Appearance of thermostable antibody in response to treatment with pollen extract.

One can note from Fig. 3 the response in terms of thermostable antibody to an injection of 10,000 units of ragweed extract in an individual on perennial therapy. There was no ragweed pollen in the air at this time (July), and there were no symptoms. In this case, there was an immediate drop before the rise in titer. It was for this reason that bloods obtained for comparison of antibody

titer were always taken previous to injections with pollen extract. This demonstration could have bearing on the use of seasonal therapy. If it can be established that the titer of thermostable antibody in the blood may be an index of successful treatment, temporary depression of this antibody during the season as result of injections may contradict the validity of continuing treatment during the pollinating season. It is of interest that there was a great fluctuation in thermostable antibody titer during the pollen season no matter whether treatment was continued or discontinued at the onset of the season (Fig. 3).

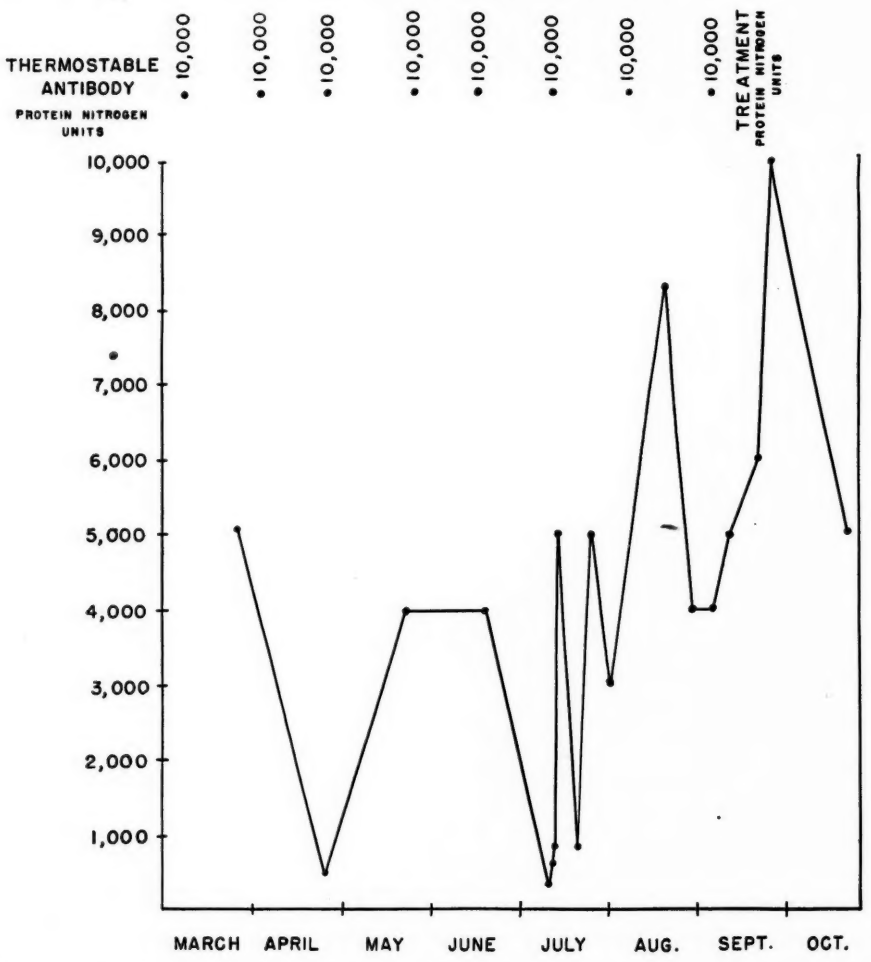


Fig. 3.—Variations in titer of thermostable antibody response to perennial treatment with pollen extract.

Traces of thermostable antibody were found to appear in the seasonal sera of both the untreated hypersensitive patients and normal untreated individuals. Conceivably, the amount of pollen antigen in the air or in the blood at any given time may influence the titer of the thermostable antibody on that date.

TABLE II. COMPARISON BETWEEN THERMOSTABLE ANTIBODY TITER IN RAGWEED SENSITIVE PATIENTS TREATED WITH RAGWEED ANTIGEN AND (1) SYMPTOMS, (2) TOTAL TREATMENT DOSAGE, AND (3) CIRCULATING ANTIGEN

TYPE*	HIGHEST TITER THERMOSTABLE ANTIBODY (PROTEIN NITROGEN UNITS)	TOTAL SYMPTOM SCORE DURING SEASON†	TOTAL DOSAGE RAGWEED ANTIGEN (PROTEIN NITROGEN UNITS)	TOTAL CIRCULATING ANTIGEN (TOTAL VOLUME PRECIPITATE IN CUBIC MILLIMETERS)
P	10,000	1	64,000	0.14
P	8,000	1	78,000	0.06
A	8,000	2	48,940	0.04
P	8,000	4	3,080	0.075
P	7,000	2	15,950	0.05
A	7,000	3	37,395	0.14
P	7,000	5	19,400	0.05
A	6,000	4	24,963	0.006
P	6,000	15	4,710	
P	5,000	11	27,400	
P	5,000	14	10,200	0.11
A	3,000	8	33,080	0.01
A	3,000	11	4,179	0.06
A	2,000	6	21,540	0.10
A	2,000	10	7,550	0.06
A	2,000	7	5,417	0.15
A	2,000	10	275	
A	2,000	11	131	0.062
A	1,000	11	97	0.07
A	1,000	12	69	0.29
A	600	12	21,630	0.05

*A = Annual treatment; P = perennial treatment.

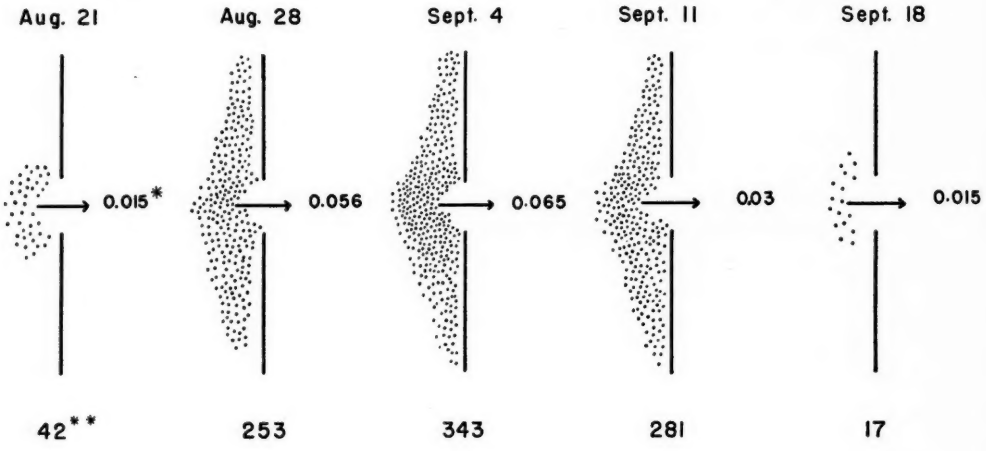
According to results recorded in Table II, the relief from hay fever is suggestingly related to the elevated titer of thermostable antibody. However, these cases are far too few to be other than suggestive.

If, however, further experience should confirm the fact that clinical improvement is related to high titers of thermostable antibody, one may predict, by analysis of blood samples during preseasonal or perennial treatment, the effect of such treatment. When a high value of thermostable antibody is attained, dosage only sufficient to maintain it would be indicated. For low values, some modification of treatment may be desirable in an attempt to raise the titer.

Although patients with the highest titer of thermostable antibody had the best clinical results, there is no evidence whatever that thermostable antibody alone is responsible for such improvement. Cooke[6] emphasized the multiplicity of antigens involved in the therapeutic use of whole ragweed extract and pointed out that detailed investigations of the antigenicity of pollen extract fractions are necessary before any conclusions can be drawn as to the importance of thermostable antibody as a factor in clinical immunity. The processes involved are far too complex and too little understood to warrant inferences. We may look upon thermostable antibody titer merely as a good index of the processes involved that produce clinical improvement.

Circulating Antigen.—In a previous communication, we reported[1] that the presence and quantity of circulating antigen correlated directly with symptoms. On the basis of these findings, we considered the possibility that circulating antigen may contribute substantially to symptoms.

However, the sera used during the 1944 study were from many different individuals, and no attempt was made to obtain a series of blood specimens from the same individual as was done in 1945. We now find that the amount of circulating antigen is apparently not responsible for severity of symptoms (Table II), but that circulating antigen and symptoms are each dependent upon the pollen count. Fig. 4 shows diagrammatically how pollen antigen on the outside of the tissue barrier is related to its presence in the blood. It is of interest that of 40 individuals studied during the season, 37 at some time showed circulating antigen.



* Average weekly circulating antigen (in terms of average volume of precipitate)

** Average weekly pollen count

Fig. 4.—Relationship between concentration of pollen in the air and circulating pollen antigen.

In contrast to last year's findings, there was no significant difference in amount of circulating antigen for the treated and untreated cases and normal controls. It would seem that, when pollen appears in the air, symptoms occur in the hypersensitive nonprotected individual and also, at the same time, circulating antigen appears in the blood of both sensitive and non-sensitive individuals regardless of treatment or symptoms.

Frequency curves were drawn for circulating antigen and symptoms, thermostable antibody titer, and reagin titer, and no correlation was observed. Moreover, there were individual variations in initial appearance, seasonal fluctuations, and disappearance of circulating antigen, and none of these variations in any way paralleled changes in thermostable antibody, reagin, or symptoms.

It is realized that the term antigen (circulating antigen) used here is that which is specifically precipitinogenic to antiragweed rabbit serum. Whether or not it is a fraction of ragweed extract that is also antigenic for thermostable antibody is unknown.

Reagin.—The possibility that circulating antigen or thermostable antibody may have had bearing on reagin titer was investigated. None was found.

There were individual fluctuations in titer of reagins with seasonal and post-treatment sera. Some (25 per cent) showed consistent slight increases, some (25 per cent) slight decreases, and others (50 per cent) remained unchanged.

There was no correlation between reagin titer and circulating antigen, or between reagin titer and thermostable antibody. Moreover, fluctuations in values of thermostable antibody or free antigen were not accompanied by corresponding changes in reagin titer.

SUMMARY

1. The relief of ragweed hay fever in this limited series of cases was usually associated with elevated titer of thermostable antibody.

2. The titer of thermostable antibody was not directly related to the amount of specific treatment. There was marked individual variation.

3. Circulating antigen during the pollen season is a phenomenon which occurs in normal individuals and in both treated and untreated patients. It is related to pollen concentration in the air. Contrary to our earlier studies, circulating antigen, as determined by present methods, apparently did not cause symptoms, and need not be considered important in the treatment of hay fever.

4. Values of circulating antigen and thermostable antibody did not correlate with reagin titer.

5. From this small experience, it would appear that perennial treatment gave better results than preseasonal injections.

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Symposium on Infectious Asthma

(Concluded)

THE TREATMENT OF RESIDUAL LYMPHOID TISSUE IN THE NASOPHARYNX BY RADIUM*†

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THE history of the development of this procedure marks an epoch in the life of a great university and its hospitals. Early in the twentieth century Dr. S. J. Crowe conceived the idea that a laboratory should be established in the Johns Hopkins University for the study of the causes and prevention of deafness. In 1924 Dr. Crowe began those investigations that revolutionized the management of deafness, and unexpectedly opened up a new field in the treatment of upper respiratory diseases. The plan of his investigation was patterned after that used in general pathology, i.e., the correlation of impaired function determined by clinical tests with location and nature of the causal lesion. Fourteen years of systematic adherence to this plan yielded 15,000 patients, 3,000 of whom were children, whose records of hearing illustrated every type and every degree of deafness and resulted in conclusions that could not have been forecast (Crowe and Baylor[1]). The hearing tests were accurately determined by the Bell Telephone Laboratories' audiometer with a range of tones from 32 to 16,384 double vibrations a second. By this instrument the investigators discovered that impaired hearing for high tones is extremely common in children as well as in adults. Examination of the nasopharynx by the nasopharyngoscope revealed the reason for the child's failure following tonsillectomy and adenoidectomy to regain the hearing of high tones: Lymphoid tissue that could not be removed by surgical procedure remained in the nasopharynx.

During childhood the lymphoid tissue in the throat reacts to infection by increasing in size and spreading to areas of the mucous membranes normally free from any lymphoid tissue. In brief, there is an overgrowth of lymphoid tissue in the nasopharynx. Children who had failed to regain their hearing after the tonsils and adenoids had been removed showed a condition in the nasopharynx identical with the condition known as granular pharyngitis, for, in the latter, numerous nodules of lymphoid tissue on the lateral and posterior walls of the pharynx are also present. These children had an overgrowth of lymphoid tissue in and around the pharyngeal orifices of the Eustachian tubes. By obstructing these tubes, this growth of tissue caused hypersecretion of mucus. This excess mucus further impaired the function of hearing and produced irritation throughout the tubes and in the middle ear.

The earliest symptom of partial obstruction is impaired hearing for the tones between 10,000 and 16,000 double vibrations. To understand speech,

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†Read at the Second Annual Meeting of the American Academy of Allergy, Chicago, Ill., Dec. 11, 1945.

good hearing in the middle of the scale from 250 to 3,000 double vibrations is essential. Until hearing for the middle tones becomes impaired, children with partial tubal obstruction have no difficulty in hearing at home or in school. Nevertheless, if untreated, deafness progresses by involving one octave after another toward the low end of the scale and becomes evident only after the tones in the speech range have been affected.

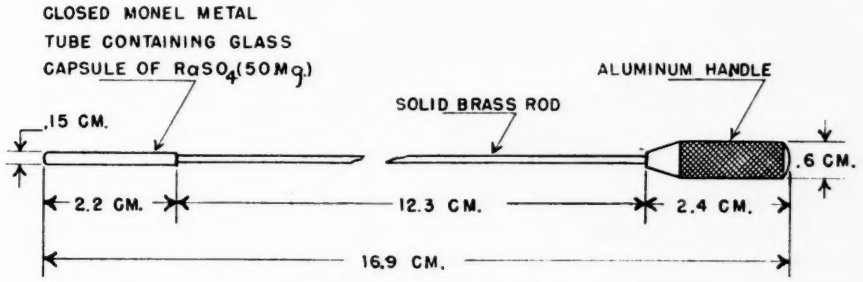

Fig. 1.—Radium applicator.

It became obvious to Dr. Crowe and his associates that the prevention of deafness depended upon the elimination of this lymphoid tissue that could not be removed surgically. The natural question arose: How can this excess tissue be eradicated? The work of Heineke of the University of Leipzig, published in 1905, showed that, except for the sex cells, lymphoid cells are the most susceptible cells to beta and gamma irradiation. Furthermore, his report showed that epithelium, muscle, and bone adjacent to the lymphoid tissue were not so susceptible to the power of irradiation as was the lymphoid tissue. This hypersusceptibility suggested to Dr. Crowe the use of radium for the elimination of surplus lymphoid tissue. For twenty years this therapeutic agent, radium, and its emanation radon have been used locally in the nasopharynx. Observation of hyperplastic lymphoid tissue under this treatment led Dr. Crowe to believe that, like skin cells, lymphocytes have a brief life cycle, probably not more than two weeks. Safe doses of radium do not destroy or totally remove lymphoid tissue, but they do reduce its size and inhibit its growth until the germinal centers are destroyed and the cells die. The effect of irradiation is to inhibit mitosis in the germinal centers, thus formation of new lymphocytes is precluded; consequently, the mass shrinks slowly until no more lymphocytes remain and the nasopharynx is covered with smooth mucous membranes.

With the aid of Dr. Curtis F. Burnam, a very convenient applicator has been developed (Fig. 1). This applicator is similar in size and shape to a nasopharyngoscope. It contains a glass tube filled with radon which is screened by a surrounding brass tube 1 mm. in thickness. Filtration through it removes all alpha rays and a large portion of the beta rays. The actual mixture of rays emitted through the applicator is 95.5 per cent gamma and 4.5 per cent beta ray.

The radon strength is between 500 and 800 millicuries. Because radon loses about one-sixth of its strength every twenty-four hours, the container must be removed once or twice a week for recharging. In each application, between 1.8 and 2 gram minutes of irradiation are administered to the areas to be

treated. The irradiation should never be undertaken if an acute pharyngitis is present, and treatment should not be repeated until from four to six weeks later. Dr. Crowe found that the duration of exposure depends upon the amount of active material contained in the applicator. With 1,000 millicuries, the time is only two minutes on each side; with 100 millicuries, twenty minutes on each side; with 50 millicuries, forty minutes on each side. In recent months, a convenient applicator containing 50 mg. of radium (not radon) may be purchased.* The life of this amount of radium is approximately a century.

The effectiveness of radiation on any tissue depends upon the amount of absorption by the tissue. Rays which go directly through the tissue have no effect. In the mixture that is used, the effects are probably (equally) divided between the gamma and beta rays. If so, this is due to the fact that all the beta rays are absorbed but only a small per cent of the gamma rays can be absorbed. These two hyperactive elements, radium and radon, act in exactly the same manner. Radium, unlike radon, is permanent and no renewals are required; however, it has the disadvantage of loss by breakage or by theft.

The otolaryngologist who tests the hearing and examines the nasopharynx can use the radium applicator by placing it on the exact spot where treatment is most needed. The radium applicator is small enough to pass along the floor of the nose of an infant, and no anesthesia is necessary.

In 1941 Dr. Crowe and his associates observed 1365 school children, between the ages of 8 and 14 years. At various hospitals in Baltimore, tonsils and adenoids had been removed from 795 of these children. More than 75 per cent had a marked recurrence of adenoid tissue in the nasopharynx, not because of poor surgery in the original operation but because of the tendency of lymphoid tissue to recur on the mucous membranes. This tissue cannot be removed in its entirety by any surgery, because it is not possible to denude the nasopharynx of the mucous membrane. Repeated surgery is useless; irradiation is the only treatment for this recurring condition. When this accumulation of lymphoid tissue is overlooked the ears are the organs that most likely will suffer. From the knowledge obtained by this group of scientists, one can conclude that it is just as important for the otolaryngologist to examine the nasopharynx and the tympanic membrane for the preservation of hearing as it is for the dentist to examine the teeth for their preservation. The loss of high tones is the first evidence of impaired hearing. The earlier it is discovered, the more opportunity there is to restore the hearing.

It is the location, not the size, of lymphoid tissue that is the important consideration. Location in and around the tubal orifices means that the obstructing nodules of lymphoid tissue cannot be removed surgically without further damaging the tubes. Infected adenoids ought to be removed surgically, and at the time of operation the first irradiation should be given. This combination of treatment not only decreases in size any remaining lymphoid tissue, but also reduces the susceptibility to further infection. Lymphoid tissue is so sensitive to radium that one need have no fear of scarring or of atrophic changes in the nasal mucosa. This initial dose is so small that, with proper application, complications cannot ensue. Usually the second treatment is given four weeks

*American Radium Corporation.

after the first; the third treatment, four weeks later. However, examination of the nasopharynx by the nasopharyngoscope will decide the need for continued treatments.

When the study of the causes of deafness began, it was anticipated that collateral problems might be encountered and affected in some manner by irradiation. The relation of infected tonsils and infected adenoids to bronchial asthma had been recognized for many years, and removal was advised whenever the indication was encountered. As mentioned above, the complete removal of adenoids is impossible; therefore, the observation made by Dr. Crowe and his associate, Dr. Ward, is apposite at this time. They observed that many of the children who were deaf for the higher tones also had bronchial asthma. Many of these children were allergic to the usual inhalants, but had failed to respond either to desensitization or to removal of the allergic agent. These children had a history of recurring colds associated with asthmatic attacks. Their nasopharynx contained numerous islands of infected lymphoid tissue, and Dr. Crowe and his co-workers noted that the severity and the frequency of the attacks became less; in some cases ceased to occur. This beneficial effect might have been due to reduction in secretion, to decrease in the absorption of allergic substances by nasal and nasopharyngeal tissue, or to removal of the nasopharyngeal "culture tube" in which sensitizing bacteria thrive.

I had the opportunity to observe these children before and after treatment, and I am convinced that the child who has frequent winter colds and an asthmatic bronchitis associated with these infections derives dramatic relief from a properly spaced course of radium therapy. It is wise to complete the treatment during the summer, for then the infections of respiration are not so prevalent, and treatment is less likely to be interrupted. A child who is sensitive to some allergen, such as the dust of his environment or to a more specific agent, orris root (talcum powder), may give disappointing results from the usual desensitization treatment because of the secondary infection in the residual lymphoid nodules. Irradiation in this group, likewise, is of great assistance. When used in conjunction with specific desensitization therapy, irradiation has completely relieved many of these patients of their disturbing symptoms. Cough due to the postnasal drip is dramatically relieved. Therefore, when the physician encounters a persistent cough in the child or young adult, he should at once resort to nasopharyngoscopic study. This may reveal the need of radium therapy. The nasopharyngoscopic study should not be overlooked in the routine examination of any patient suffering from respiratory disease. I have elaborated on this epochal work because, although it has a most important bearing on this entire respiratory problem, especially on the treatment of bronchial asthma, no mention of it appears in any publications on the treatment of allergic disease. A detailed report of the treatment of the asthmatic child by radon and radium will be made at one of the future meetings of this Society.

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TREATMENT OF INTRACTABLE ASTHMA*†

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IN PRESENTING physiologic therapy and more recent attempts to institute antibiotic treatment in intractable asthma, I wish first of all to emphasize the importance of a continued investigation of the allergic factor that may be responsible for maintenance of persistent bronchial spasm. A careful history may elicit seasonal variations that give a clue to the possibility of pollen asthma. In the late fall sudden exacerbation of bronchial spasm may be related to the turning on of steam heat in boxed-in radiators or in hot air furnaces in which an unsuspected circulation of dust may take place. Removal of slip covers from upholstered furniture that contains horsehair is at times an unforeseen source of recurrence of asthma. These are but a few of the many possible etiologic factors, which include food allergy as well as the response to hidden infection.

Intractable asthma and status asthmaticus were, a few years ago, characterized by a progressive lack of response to administration of epinephrine. Due to the widespread use of aminophyllin, developed because of its initial efficacy in terminating refractoriness to adrenalin, many patients are now observed in whom the asthmatic state is only partially controlled by both drugs, since refractoriness may develop to aminophyllin as well as to epinephrine.

The treatment of these patients rests on an understanding of the pathologic physiology of persistent bronchial spasm. Overinflation of the lungs is to some degree present in every patient with persistent bronchial spasm. In the absence of organic pulmonary emphysema, the negative intrapulmonary pressure during inspiration is pathologically elevated, which is associated with congestion and edema in the bronchial mucous membrane as well as an abundant expectoration of mucus. The pathologic situation under these circumstances is not simply one of spasm of the bronchial constrictor muscles, but that of narrowing of the smaller bronchi as the result of inflammatory or edematous swelling of the wall.

Measures which decrease the elevated intrapleural negative pressure include those that decrease the minute volume of respiration and those which increase the lumen of the respiratory passageway. Administration of oxygen-enriched atmospheres, in conjunction with the drugs such as demerol, provides the simplest method of restoring responsiveness to broncho-dilator medication. The inhalation of a concentration of 40 to 50 per cent oxygen by a catheter inserted in the nasal or oral pharynx, a head tent or body tent is generally preferable to the mask, the latter method being frequently found uncomfortable for continuous therapy. The use of oxygen for a period of a week is at times followed by a remission in intractable asthma, especially when curtailment of epinephrine and aminophyllin is gradually obtained.

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†Read at the Second Annual Meeting of The American Academy of Allergy, Chicago, Ill., Dec. 11, 1945.

Since demerol by intramuscular injection is frequently followed by bronchial as well as central nervous system relaxation, this drug appears to be preferable to morphine and its derivatives. Respiratory depression has been observed as the result of morphine administration with a fatal outcome in a sufficiently large number of cases as to constitute a warning against its use. The side-effects of demerol—nausea, dizziness, and vomiting—must be carefully controlled in order to prevent a premature abandonment of a remedy as vaulable as this one frequently is. Instead of giving 100 mg. by injection, it is often desirable to administer 50 mg. and to allow an hour or two hours to elapse before the second dose of 50 mg. is repeated. In this way the drug can be used night and morning, or in 50 mg. doses, for acute paroxysms of asthma. Additional sedation is generally achieved by phenobarbital in dosages of 0.03 Gm. two or three times during the day, and 0.1 to 0.2 Gm. at night rather than barbiturates, such as sodium amytal, nembutal, or seconal, since the latter at times produce an irrational state if sleep is not immeditely obtained. In the attempt to discontinue adrenalin and aminophyllin temporarily, other drugs may be employed, such as $\frac{1}{150}$ to $\frac{1}{100}$ grains of atropine two or three times daily. The recent introduction of benadryl and pyribenzamine makes it possible to employ these for empirical trial. Administered in 50 mg. doses by mouth three to five times a day, they are helpful in a small percentage of cases, apparently especially those in which pollens may be a factor in the etiology of the condition. The side-effects of the drug—dizziness, jitteriness, or somnolence—interferes with their continued use in some cases.

Intermittent inhalation of 80 per cent helium and 20 per cent oxygen mixtures has been employed to decrease the effort of breathing, lower the pathologically elevated negative intrapleural pressure during inspiration, and to achieve a better ventilation of the alveoli through constricted bronchi. This may be carried out by employment of a mask for periods of one-half to one hour three to six times a day for four or five days, or it may be given in a closed head tent now available with a transparent canopy that makes closure about the neck. When the helium-oxygen hood is available, a positive pressure of 4 to 5 cm. may be continuously utilized in conjunction with helium-oxygen inhalation, or with the employment of 100 per cent oxygen. The positive pressure facilitates inspiration by gently forcing the therapeutic gas through constricted bronchi during inspiration and maintains a more patent lumen during expiration. The hood is employed generally for periods of two hours two or three times a day, in severe cases more continuously.

The positive pressure mask now available for administration of either helium-oxygen mixtures or pure oxygen provides a positive pressure in expiration only and is, therefore, more suitable for the treatment of pulmonary edema. In combating the dyspnea of intractable asthma, positive pressure should be maintained during both inspiration and expiration. During the war a demand type of regulator was developed for application of continuous and intermittent positive pressure, an assembly which may subsequently be adapted to clinical use. The disadvantages of this type of equipment are not only the expense of

the valve, but the requirement for almost constant personal supervision. The positive pressure hood is probably the most effective method of applying continuous pressure during inspiration and expiration, but trained technical supervision is also necessary, although not continuous personal attendance.

Of the measures employed to increase the patency of the bronchial tree, inhalation of the nebulized solution of 1:100 or 1:75 epinephrine together with 1 per cent neosynephrine, 0.5 c.c. of each solution, at times accomplishes a substantial degree of bronchial dilatation and broncho-vasoconstriction when hypodermic injection of adrenalin is of comparatively little value. The use of a cylinder of 80 per cent helium with 20 per cent oxygen to nebulize these drugs is *especially* helpful in some cases, since the lighter-than-air gas carries the aerosol into the smallest bronchioles. The inhalation may take place through the conventional nebulizer, preferably one that produces particles which are mostly under one micron in diameter. A more economical and efficient use of aerosols is provided by the penicillin aerosol rebreathing apparatus, in which a rubber bag is employed to re-breathe the therapeutic gas as well as the nebulized bronchodilator drugs. The 2 c.c. ampule of aminophyllin containing 0.48 Gm. may also be emptied into the nebulizer and used as an aerosol. Although it has a bitter taste, it is at times convenient to administer it by nebulization. Coughing and elimination of sticky mucus often follows these inhalations, with marked relief of dyspnea.

The large number of miscellaneous procedures employed in the treatment of intractable asthma may not be extensively reviewed here, but the employment of a few of them will be commented upon. Intravenous injection of 50 c.c. of 50 per cent glucose every day or every other day three or four times has definitely appeared to be helpful in some cases. Glucose is also used, especially in dehydrated cases, in concentrations of 5 per cent, 1,000 c.c. being given in a slow infusion daily for two or three days. Aminophyllin, 0.48 Gm. to 0.7 Gm., may be added to the one-liter glucose flask. If iodides have not previously been employed, benefit may follow the administration of 1 c.c. of a saturated solution of potassium iodide three or four times a day for the first week of intensive therapy directed at bronchial relaxation.

Anesthesia with ether is followed in some cases by an abrupt and satisfactory remission of intractable asthma. It has been given rectally in dosages of 80 to 90 c.c. mixed with equal amounts of olive oil, or it may be given by inhalation over a period of thirty to forty minutes. Deep anesthesia at times results in bronchial relaxation, more generally observed twenty-four hours afterward than immediately. The use of ether may be required two or three days after the first treatment; rarely, three exposures to anesthesia are employed.

Bronchoscopic suction of retained secretions is a measure that is also followed by marked relief in certain patients with status asthmaticus. The temptation to hurry through the bronchoscopic therapy should be resisted, as the best results are obtained when a thorough suction of the bronchial tree on both sides is carried out. In the experience of the author, ether anesthesia and bronchoscopic aspiration have been combined at times with excellent results, since both

bronchial relaxation and elimination of mucous plugs are achieved at the same time. It is important that the aftercare of the patient who has been subjected to ether includes the conventional measures which prevent the tongue from falling backward into the throat, namely, placing the patient on the side with the head of the bed not elevated, and with a pharyngeal airway in place until consciousness returns.

Artificial fever is required in some patients who do not respond to other measures. The maintenance of a temperature of 103° to 105° F. for two to three hours in a fever cabinet, repeated once or twice at two- or three-day intervals, has, in a number of instances, been responsible for the termination of a persistent asthmatic state. Fever therapy may also be produced by intravenous injection of typhoid vaccine. When this method is used, it is better to instill 0.3 c.c. of triple typhoid vaccine into a liter of 5 per cent glucose and employ it as a slow infusion. When a chill with a rise in temperature takes place, the infusion may be still further slowed, or it may be temporarily stopped. Better results are obtained when the temperature is allowed to persist for three to four hours than when the treatment is permanently interrupted after the chill.

In patients with bronchial asthma and pulmonary emphysema, manual elevation of the diaphragm, as suggested by Dr. Gay, is often followed by subjective relief as well as an increase in vital capacity of from 200 to 1,000 c.c. The procedure is best carried out after preliminary inhalation of nebulized epinephrine. The palms of the hands are placed underneath the ribs and pushed upward and inward during the latter half of expiration. The escape of trapped air may frequently be heard as a wheeze. When bronchial spasm persists, the lungs soon become overinflated again. However, in some cases, the relief is sufficiently marked as to warrant the use of this measure, which may be readily taught to the nurse, and later to the patient himself. It has been found of especial value in organic pulmonary emphysema.

The trial of antibiotic therapy in so-called infectious asthma has been stimulated by the introduction of penicillin. Many reports, both favorable and unfavorable, have followed its employment by intramuscular injection as well as by inhalation as an aerosol. We are in the process of evaluating the results of inhalation of penicillin aerosol in approximately 200 cases of bronchopulmonary disease, including chronic bronchitis, bronchiectasis, lung abscess, and bronchial asthma. The treatment of sinusitis by nasal inhalation of penicillin aerosol in conjunction with repeated negative pressure applied to the nasal passages has been one of the most encouraging features of this investigation. By means of an especially constructed valve, a suction pressure of 50 to 70 mm. Hg is repeatedly developed in the antra and other sinuses. When the pressure returns to that of the atmosphere, penicillin aerosol in the nasal passages is aspirated into the sinus cavities. Cases of chronic as well as acute sinusitis have shown marked improvement in some instances as the result of treatment over a period of one to three weeks with this device. In some patients with severe bronchial asthma, relief from persistent bronchial spasm followed the clearing

of infection in the sinuses. In fact, this method of treatment appears to be applicable to a considerable number of cases in whom radical surgical measures are not feasible.

When penicillin aerosol is administered for the treatment of bronchial infection, it may be inhaled through a glass mouthpiece or through a mask, in either event in conjunction with a two-liter rebreathing bag and a nebulizer that produces particles of small size. The concentration employed is generally 50,000 units in 1 c.c. of normal saline or distilled water; the *crystalline* sodium salt should be used rather than the ordinary sodium or calcium preparation of penicillin. Humidification of the aerosol is accomplished by placing a glass of hot water in the rebreathing bag, which itself is then deposited into a container of hot water. Four to five inhalations a day, at times accompanied by an oral or injected dose of penicillin at night, are administered for a period of approximately two weeks. In approximately one-third of the cases, either marked or significant moderate benefit has been observed. In patients with hemolytic streptococcus or pneumococcus infection, relief is more likely to take place than in those in which the predominating organism is described as *Streptococcus viridans,* although marked improvement has also been noted in some cases with this apparent type of infection.

In about one-half of 40 patients who have been treated either with penicillin aerosol administration by oral inhalation or by the treatment of sinusitis, the moderate or marked improvement initially observed has been maintained for a period longer than two months. In the remainder, a partial or complete recurrence of symptoms has been observed. It would appear on the basis of admittedly insufficient evidence, that patients who have been treated with penicillin, and later with conventional hyposensitization therapy with catarrhal vaccine and dust, do better than those in whom a single course of treatment is given without any follow-up therapy. In a few cases, significant as well as specific improvement as the result of penicillin areosol has lasted as long as one year following the initial treatment. Although the results of antibiotic therapy with penicillin in other cases of bronchial asthma are frequently disappointing, sufficient therapeutic value appears to have been demonstrated in some cases as to justify further trial of the method.

The difficulties of appraising the therapeutic efficacy of any procedure in bronchial asthma are too well known to permit of a definitive evaluation of this particular technique. The most conspicuous and unquestionable results have been the effect of nasal penicillin aerosol administration in conjunction with intermittent negative pressure in the treatment of infectious sinusitis. Although the bacterial factor in infectious asthma is frequently clouded by the existence of other allergic factors, the causal relationship between infection in the sinuses and persistent bronchial spasm has, in our experience, been more clarified by the aerosol negative pressure treatment of sinusitis than by the use of operative measures to promote drainage from the sinuses. When surgical procedures are carried out, other factors may be involved in the termination of an asthmatic state, such as anesthesia, fever and the nonspecific effects of tissue trauma. How-

ever, the clinical and roentgenologic evidence of disappearance of chronic sinus infection as the result of a technique that does not utilize the above-mentioned physiologic changes makes it possible to form a tentative conclusion of a specific effect of sinus infection in those cases in which a state of intractable asthma is relieved coincident with disappearance of infection in the sinuses. It is possible that the physical effect of negative pressure on the mucous membrane of the nasal passages may in itself have some reflex effect on bronchial spasm. However, when the clearing of infection is followed by diminution of congestion, inflammatory swelling and nasal discharge, this sequence of events would more legitimately argue for a specific effect of penicillin on the infectious process. In cases of combined etiology infection as well as allergy to dust and other substances, the results are inevitably less clear-cut. As far as inhalant allergy is concerned, residence in a filtered air room would appear to be the best method of eliminating this factor. Electrostatic precipitation of dust, pollens, and other air-borne substances appears to be the most efficient method, although simpler filters may be employed for this purpose, provided that adequate demonstration of their filtering efficiency has been given.

A combined therapeutic program may be necessary in patients who are sensitive to a multiplicity of substances. Under these circumstances, physiologic and antibiotic therapy, diet, the use of the anti-histamine drugs, and hyposensitization may all be indicated to such an extent as to tax the patience of the physician as well as the cooperation of the patient.

Special Reports

THE GENERAL ADAPTATION SYNDROME AND THE DISEASES OF ADAPTATION

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(Concluded)

FACTORS INFLUENCING THE COURSE OF THE GENERAL ADAPTATION SYNDROME

One of the most important factors influencing the course of the general adaptation syndrome is the *stage of adaptation* of the organism at the time when it is confronted with an alarming stimulus. Thus, immediately following an alarm reaction produced by one evocative agent, neither this nor any other such stimulus can elicit this reaction again. On the other hand, when a high degree of adaptation has been acquired to one agent (the "stage of resistance" of the general adaptation syndrome) exposure to a different stimulus finds the organism particularly irresistant, so that it responds with a marked shock phase.[313, 374-376, 409, 556] Besides the previously mentioned examples of loss of adaptability to new conditions during the stage of resistance elicited by one particular alarming stimulus, many additional illustrative instances could be mentioned. Thus, it was found that mice, highly adapted to ultraviolet rays, become exceedingly sensitive to acetonitrile[174]; morphine addicts who have developed a great tolerance to this drug are hyperreactors in the "cold-pressor test,"[274] et cetera. Other examples given earlier in this review indicate that during the countershock phase of the alarm reaction both specific and nonspecific resistance tends to rise above normal. Unfortunately, however, as we have said before, so many factors influence resistance that it is almost impossible to ascertain in any specific case whether a change in resistance is solely due to the development of a general adaptation syndrome.

After *adrenalectomy*[542, 545, 601] or *hypophysectomy*[542, 545] the shock phase is particularly severe and the countershock phase is negligible or absent. Even relatively mild alarming stimuli such as the folliculoid hormones cause severe shock-phase symptoms in the absence of the adrenals or the pituitary.[566, 596]

The hypoglycemia is particularly marked and the hyperglycemic peaks are negligible if present in adrenalectomized[554] and hypophysectomized[588] animals. This is probably due to the fact that in hypophysectomized or adrenalectomized animals glucose is not readily produced from endogenous sources.

Exposure to nonspecific damage also causes particularly marked hypochloremia which is not followed by a second hyperchloremic countershock phase in adrenalectomized animals. It is noteworthy, furthermore, that in the absence

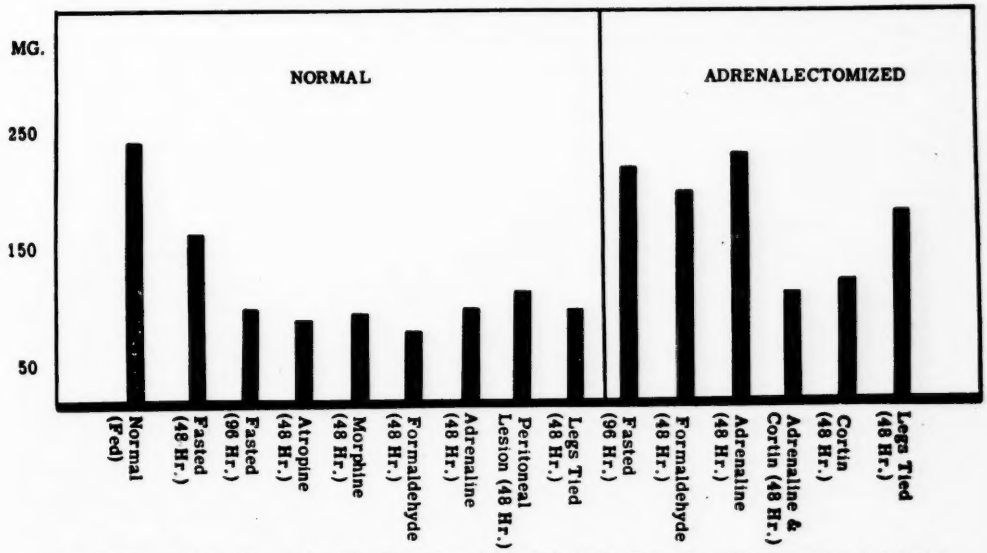
of the adrenals the hyperchloremic response peculiar to muscular exercise is reversed to the hypochloremic type common to all other alarming stimuli.[554]

The lipid deposition in the liver, occasionally seen during the alarm reaction, is prevented by adrenalectomy.[362, 363]

The thymus and, to a lesser extent, the other lymphatic organs fail to involute in adrenalectomized[155, 156, 200, 284, 360, 361, 542, 624] or hypophysectomized[201, 542, 545] rats, although all other signs of the alarm reaction are particularly severe in such animals. Even the well-known x-ray atrophy of the thymus and other lymphatic organs is prevented by adrenalectomy unless huge doses are administered[680] or the rays are applied directly to the thymus.[361, 362] Regeneration of the thymus after x-ray exposure is accelerated by adrenalectomy.[241a]

Prevention by Adrenalectomy of Thymus Atrophy Normally Seen During Alarm Reaction in the Rat.*

(The black areas indicate the weight of the thymus under various experimental conditions and have been obtained from averages of large groups of rats.)



* Slightly modified after: Selye, H.: Thymus and Adrenals in the Response of the organism to Injuries and Intoxications, Brit. J. Exper. Path. 17: 234, 1936.

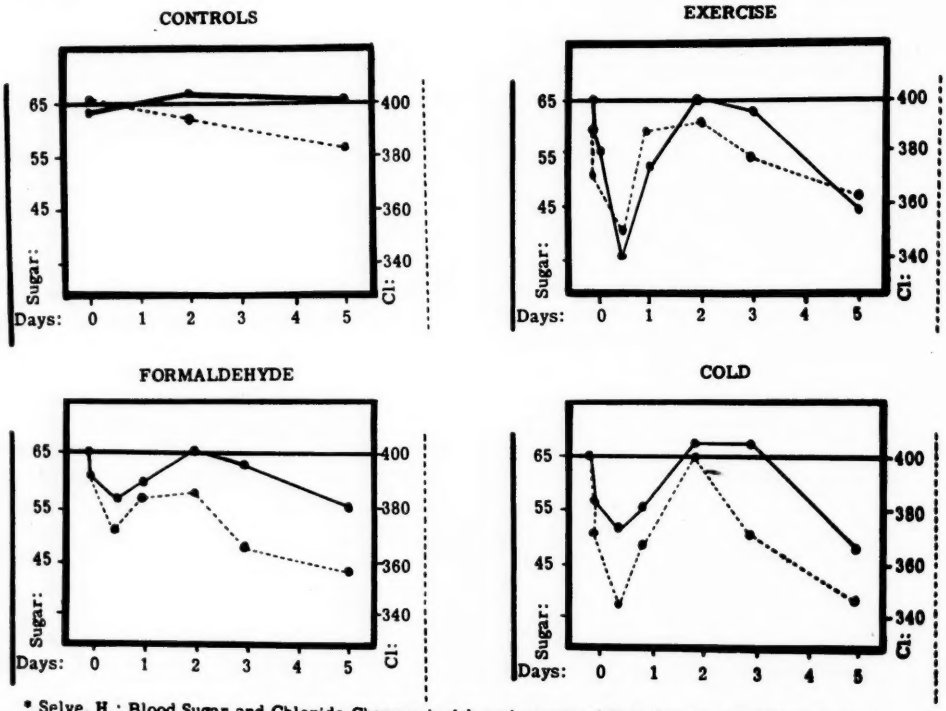
Plate XVII.—Prevention by Adremalectomy of thymus atrophy, normally seen during alarm reaction in the rat. It will be noted that, in the intact animal, various nonspecific damaging agents, including prolonged fasting, cause involution of the thymus while adrenalectomy prevents this reaction. Among the agents studied here, only cortical extracts caused thymus involution after adrenalectomy. All animals (except the first group which acted as a control) were fasted throughout the experiment and the length of the exposure is indicated in parentheses, with each group.

The low resistance of patients suffering from *status thymicolymphaticus* is brought to mind by these observations, since in this disease enlargement of the thymus and adrenal hypoplasia are combined with particular sensitivity to sudden stress.

Corticoid hormone treatment produces thymus involution even in adrenalectomized or hypophysectomized animals and simultaneously improves their re-

sistance to alarming stimuli; however, larger doses are required for this than for the mere maintenance of life.[284, 286, 542, 545, 601] Adrenalin is ineffective in causing thymus involution after adrenalectomy.[542]

It should be mentioned in this connection that estrone, estradiol, testosterone,[242a, 525, 596] and diethylstilbestrol,[598] i.e., compounds with male or female sex hormone activity, are also capable of producing thymus involution even in the adrenalectomized animal. Since the adrenal cortex contains both folliculoids and testoids it is not impossible that secretion of such steroids could also play some part in the production of thymus involution during the alarm reaction.



* Selye, H.: Blood Sugar and Chloride Changes in Adrenalectomized Rats During Adaptation to Various Stimuli, Proc. Soc. Exper. Biol. and Med. 38: 728, 1938.

Plate XVIII.—Whole blood chloride and blood sugar changes in adrenalectomized rats during the general adaptation syndrome. Note that, in the adrenalectomized animals, the initial hyperglycemia of the alarm reaction fails to develop while the hypoglycemic phase is particularly pronounced. The entire general adaptation syndrome appears "telescoped" into a brief five-day period, but three stages are still distinguishable. The first (alarm reaction) is characterized by hypoglycemia and hypochloremia, the second (stage of resistance) by a return of these values to normal, and the third (stage of exhaustion) by a second period of hypoglycemia and hypochloremia; this third stage ends in the death of the animal.

The characteristic lymphocytopenia of the alarm reaction is prevented by adrenalectomy.[175]

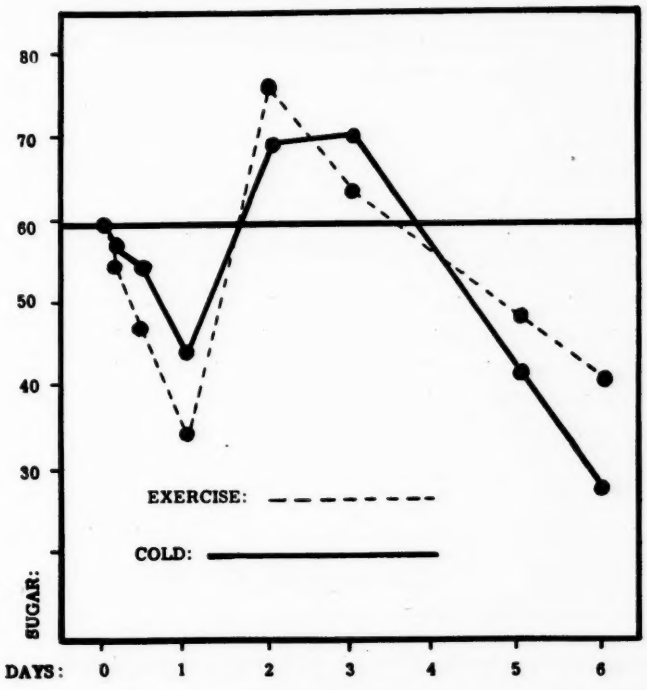
Our most recent experiments show that, in adrenalectomized rats maintained on a threshold dose of cortical extract, it is impossible to produce nephrosclerosis or myocarditis with anterior pituitary preparations. Since, under otherwise similar conditions not adrenalectomized controls develop marked nephrosclerosis

and cardiac lesions, it appears justified to conclude that the action of the anterior lobe principles is mediated through the adrenal cortex.

Unlike adrenalectomy, castration does not protect the thymus against "accidental involution" due to alarming stimuli.[695b]

It is rather curious that in *thyroidectomized* animals the blood sugar shows a particularly marked and persistent rise following exposure to alarming stimuli and after prolonged fasting the hyperglycemia of the countershock phase develops very rapidly in them.[562] This is all the more surprising since in intact,

Blood Sugar Changes in Hypophysectomized Rats During the General Adaptation Syndrome Produced by Exercise or Cold.*



* Selye, H., and Foglia, V. G.: Blood Sugar Changes in Hypophysectomized Rats During Adaptation to Various Stimuli, Proc. Soc. Exper. Biol. and Med. 39: 222, 1938.

Plate XIX.—Blood sugar changes in hypophysectomized rats during the general adaptation syndrome produced by exercise or cold. Note that hypophysectomy likewise decreases adaptability so that the general adaptation syndrome is "telescoped" into a brief six-day period under the conditions of this experiment; yet the three stages are again clearly distinguishable: hypoglycemia during the alarm reaction, return slightly above normal during the stage of resistance, and secondary hypoglycemia during the stage of exhaustion. The greatly shortened stage of resistance in the adrenalectomized (Plate XVIII) and hypophysectomized (this Plate) animal clearly shows that adrenal and hypophyseal hormones are not indispensable for adaptation but they prolong the period during which resistance is possible.

fasted animals the hypoglycemia seen during the latter stages of the shock phase is particularly pronounced.[564] Thyroidectomy also increases the severity of the hypochloremic phase and reverts the abnormal hyperchloremic response of muscular exercise to the hypochloremic type common to all other alarming stimuli.[562]

Most investigators agree that *adrenalin* exerts no important beneficial effect in shock although it may temporarily raise the blood pressure.[14, 438] The same is probably true of vasopressor *posterior lobe extracts*.[4, 53]

Some workers, who probably used unsuitable hormone preparations or otherwise unfavorable experimental conditions, concluded that, in the normal (not adrenal deficient) individual, *corticoids* are entirely ineffective in combating shock and allied conditions.[14, 51, 148, 165, 168, 196, 209, 288, 289, 296, 318-321, 336, 382, 438, 470, 509, 630] We found, however, that at least under certain conditions, these hormones can prevent shock and facilitate the development of countershock phenomena thus increasing resistance even in the nonadrenalectomized animal.[583, 584, 587] It is possible that some types of damage are better combatted with salt-active corticoids and others are better combatted with sugar-active corticoids; our first efforts to demonstrate that corticoid treatment can raise resistance above normal in the nonadrenalectomized animal indicated, however, that in general cortical extracts and pure carbohydrate-active corticoids (with oxygen on carbon atom 11) are more efficient in this respect than are the salt-active corticoids (such as desoxycorticosterone). Since the appearance of these first publications the question has received a great deal of attention and it was claimed that corticoid hormones can increase the resistance of intact animals not only to traumatic shock[349, 460, 462, 675] but also to a variety of other alarming stimuli such as excessive muscular exercise,[54, 335] colchicine,[106, 107] peptone shock,[297] intraperitoneal injection of hypertonic glucose solution,[498] potassium chloride,[383, 442, 642] water intoxication,[220, 221] histamine,[42, 474] intestinal distention,[197] menstrual toxin,[616] microbial toxins and infections,[6, 114, 218, 326, 396, 486, 612] partial hepatectomy,[584] anoxia,[27, 637] heat,[67, 391, 529] veronal,[171] toxic tissue extracts,[503] and perhaps even the type of shock produced after temporary occlusion of large vascular territories.[69, 70, 314, 315, 509, 530]

In clinical medicine the beneficial effect of corticoids is more difficult to prove, at least with the type of preparation now available. However, many investigators consider such treatment desirable in combatting shock although most clinicians agree that it should not replace but merely complement the other established therapeutic procedures, such as blood transfusion.[76, 94, 166, 252, 258, 262, 352, 353, 384, 412, 420, 483, 689]

In patients, corticoids have been claimed to be beneficial also in the treatment of celiac disease[5, 16, 283, 337, 454, 463, 534, 620]; hemoconcentration due to ether anesthesia[417, 489]; acute confusion during typhoid fever or the puerperium[280, 661]; various acute infections, especially typhoid fever and diphtheria[31, 38, 41, 48, 49, 54, 76, 149, 199, 229, 241, 244, 245, 268, 298, 393, 399, 400, 425, 453, 475, 609, 662]; psychoses[377, 378]; exhaustion due to fever therapy[164]; burns[172, 233, 253, 268, 465, 499, 689]; allergy[684a, 684b]; premature infants[25]; "fetal shock"[47]; tuberculosis[49, 102, 103, 535]; damage due to heat,[528, 529] cold,[234, 331] or x-rays[671]; et cetera.[101, 392, 667]

In connection with the low power of desoxycorticosterone to combat acute damage, it should be kept in mind that most actions of this compound tend to develop slowly and that animals chronically pretreated with it develop a pronounced "compensatory atrophy" of the adrenal cortex. Such animals whose

adrenal cortex has involuted under the influence of desoxycorticosterone pretreatment can show a slight enlargement of the adrenal cortex when exposed to alarming stimuli, but this enlargement is subnormal and functionally inadequate. Probably after compensatory atrophy the adrenal cortex is comparatively ineffective in producing the large amounts of sugar-active corticoids required during the alarm reaction and hence animals so pretreated respond to damage somewhat like adrenalectomized animals and exhibit low general resistance and marked hypoglycemia during stress.[150, 153, 294, 383, 570, 586, 587] This is probably due to the inhibitory effect that corticoids have on the formation of adrenotropic hormone by the pituitary. It is well established that excess production of the latter hormone is essential for the cortical enlargement seen in the general adaptation syndrome, since in hypophysectomized animals the cortex does not undergo hypertrophy under stress[214, 294, 542, 596] even if it is maintained by daily treatment with adrenotropic hormone.[582] It is noteworthy, however, that, unlike in mammals, in the pigeon the cortex responds to alarming stimuli even after hypophysectomy.[429, 430]

Anterior pituitary extracts may help to counteract the protein catabolic effects of nonspecific damage[118] and purified corticotropic preparations share to some extent the power of cortical extracts to raise resistance to alarming stimuli.[460, 462, 498]

Testosterone and other testoid compounds with marked nitrogen-retaining ability may also help to combat the protein catabolic action of nonspecific damaging agents.[2, 12, 37, 495, 623] It is thought that the protein catabolism occasioned by excess corticoids is inhibited by the protein anabolic or nitrogen-retaining effect of the testoids.

The beneficial action of blood or saline *transfusions* has been established in carefully controlled animal experiments[14] as well as by general clinical experience. Both corticoid administration and transfusions are physiologic types of treatment, inasmuch as they imitate the phenomena of countershock.

Dietary measures are of particular importance in influencing the course of the general adaptation syndrome. Thus, it was found that feeding or even intravenous injection of glucose can selectively prevent gastric ulcer formation in rats in which an alarm reaction is produced by spinal cord transection, exposure to cold, et cetera.[597] In these acute experiments the other manifestations of the alarm reaction (thymus and lymph node involution, adrenal enlargement, etc.) were not influenced by the glucose treatment, so that a certain dissociation of the manifestations of the reaction was accomplished.

As we shall see later, the experimental "diseases of adaptation" are likewise considerably influenced by the diet, irrespective of whether they are produced by chronic exposure to damage (e.g., cold) or stimulated by hormone (desoxycorticosterone, anterior pituitary extract) overdosage. Thus, we have found that a high intake of sodium and diets rich in protein but poor in carbohydrates greatly facilitate the production of these diseases, while "acid ash" diets, as well as food poor in sodium and protein but rich in carbohydrate, protect against them.

The fact that some agents may selectively inhibit the development of one particular manifestation helps to explain that not all the lesions characteristic of the general adaptation syndrome are proportionately developed in every individual instance.

Fasting is particularly effective in increasing sensitivity to alarming stimuli. In fasted animals, protein catabolism, gastric ulcer formation, involution of the thymus and lymph nodes, as well as the hypoglycemic phase of the alarm reaction, are especially prominent and the adrenal cortex undergoes particularly rapid and intense hypertrophy.[355, 542, 545, 564] This is hardly surprising if we remember that protein catabolic actions are especially deleterious in the absence of exogenous food supplies with which the tissues could be repaired.

If an equicaloric amount of fat is substituted for carbohydrate, there is no change in the ability of the diet to influence the production (by LAP or DCA) of the diseases of adaptation in the rat. Hence, we concluded that the low protein, and not the high carbohydrate, content of the protective diets was the cause of their efficacy. Experiments are now underway to determine whether all proteins are equally active or whether individual proteins, polypeptides, or amino acids are responsible for increasing sensitivity to the actions of corticoids and corticotropic hormones. In any case, the mechanism through which high-carbohydrate, low-protein diets protect against the "diseases of adaptation" is rather complex. Our experiments on the rat indicate that not only the sections of the corticoids on peripheral organs (e.g., heart and kidney) but even the adrenal stimulating effect of corticotropins is augmented by high-protein diets. Hence, we conclude that such diets enhance the production of the diseases of adaptation at two different steps in their pathogenesis; they augment the efficacy of both corticotropin and of corticoid steroids. This fact should also be taken into account in bio-assays for these activities.

The importance of *nervous disturbances* has often been suspected; yet comparatively little evidence has come forward to prove that the nervous system plays a prominent role in regulating the course of the general adaptation syndrome. It is well known, of course, that extensive surgical interventions on the nervous system will in themselves cause an alarm reaction (e.g., hypothalamic injuries, spinal cord transection), but this is not unexpected since such interventions, just as any other type of damage, act as alarming agents. On the other hand, it was found that the general systemic effects (gastrointestinal ulceration, pleural effusions, ascites, hemoconcentration, etc.) of thermal trauma to one hind leg were essentially the same in intact and in spinal cats.[306, 307]

Analgesic drugs are of definite value in combatting various types of shock but they must be given in moderate doses; otherwise, they prove stronger alarming stimuli than the pain and emotion which they combat.[438, 492, 539] It has been noted, furthermore, that animals under ether anesthesia appear to be more resistant to shock produced by traumatizing an artificially-perfused, enervated limb, than more deeply anesthetized animals under chloralose anesthesia.[381] Some promising preliminary experiments have been performed to prove that transection of the pituitary stalk modifies the rate of thyrotropic hormone pro-

duction in response to certain emergency situations,[142] but further work along these lines will be necessary to determine exactly what part is played by nervous connections in conducting stimuli to the pituitary and thus modifying adrenotropic hormone production. It has been claimed that denervation of the carotid sinus combats shock by increasing the endogenous production of corticoids,[364] but the evidence is inconclusive.

The commonly practiced method of combatting shock by *heat*, with the view of maintaining the body temperature at a normal level, has been claimed to be not only useless, but actually harmful, in well-controlled animal experiments.[14] In the event of an alarm reaction produced by transection of the spinal cord, however, the resulting drop in body temperature appears to represent the major shock-producing factor. This has been proved by experiments in which the body temperature of animals with the spinal cord transected was maintained by placing them in warm surroundings. Under such conditions the manifestations of the alarm reaction were greatly inhibited or completely prevented.[126, 127, 207]

Partial kidney insufficiency produced by *unilateral nephrectomy* sensitizes animals to the development of nephrosclerosis, nephritis, hypertension, and periarteritis nodosa following chronic exposure to damaging agents such as cold[574, 577]

The administration of excessive quantities of *sodium chloride* further sensitizes the body in this respect, while *acidifying salts* (e.g., ammonium chloride) tend to prevent such changes.[574] It is noteworthy that the same agents which increase sensitivity to this type of nonspecific damage (partial nephrectomy, sodium chloride) also sensitize animals to desoxycorticosterone and anterior pituitary extract, while, conversely, the agents (acidifying salts) which inhibit the toxic manifestations of these hormones are also beneficial in preventing hypertension and renal and cardiovascular lesions following exposure to nonspecific damage.[251, 599] Preliminary observations suggest that sodium restriction[246a] or treatment with ammonium chloride are also beneficial in patients with renal hypertension.[530a] These observations give further support to the concept, according to which the corresponding diseases of clinical medicine are due to the endogenous overdosage with hormones of this type, presumably elaborated for defensive purposes.

Probably many *other factors* exert some influence on the development of the general adaptation syndrome but all these can hardly be discussed here in detail. Suffice it to mention, for example, that sodium succinate injections appear to exert some beneficial influence upon traumatic shock[445] and that climatic and weather conditions are also of importance for the development of the general adaptation syndrome.[476]

THEORETICAL INTERPRETATION OF THE GENERAL ADAPTATION SYNDROME

In discussing the theories proposed to explain the various manifestations of the general adaptation syndrome, it is well to separate the theories on shock from those dealing with the other phases of this syndrome.

A. Theories Concerning the Shock Phase.—The greatest problem in interpreting the manifestations of shock is to explain why so many different agents lead to essentially the same syndrome and how an injury to a limited part of the body can effect the entire organism. Innumerable theories have been proposed in an effort to explain these two basic facts. It is not within the scope of this review to discuss all these in detail, and the following brief summary is only given as a key to the relevant literature.

1. The Theory of Impaired Circulation: Moon[435, 437] defined the shock phase as follows: "Shock is a circulatory deficiency, neither cardiac nor vasomotor in origin, characterized by decreased blood volume, decreased cardiac output (reduced volume flow) and by increased concentration of the blood." Although this definition is widely accepted, it is not valid in every case, since among other things it excludes spinal shock, which is generally considered to result from vasomotor paralysis and yet leads to the typical morphologic and chemical changes characteristic of shock.[545] It also excludes shock resulting from excessive muscular exercise, which is often accompanied by a decrease in the red cell count.[563] Allen[14] observed, furthermore, that in cases of severe experimental traumatic shock, "transfusions of blood or plasma no longer suffice to save life, even though the corpuscle count is kept at a normal or reduced level and all indications point to normal or increased blood volume together with adequate propulsion of the blood. Theories which regard these as the determining factors in shock are thus invalidated."

It has been claimed that capillary permeability is increased in all known types of shock. Be this as it may, the capillaries are extremely sensitive to damaging agents and tend to become permeable as a result of local or general disturbances, hence this symptom is hardly a suitable basis for a definition; it is no more characteristic than any other sign of damage (e.g., muscular weakness, pallor, etc.). Increased capillary permeability is also present during the agonal stage of chronic diseases, which is not generally considered to be "shock."

2. The Theory of Dehydration and Hemoconcentration: This theory is rather similar to that mentioned previously. It is based on the assumption that the symptoms of the shock phase are primarily due to dehydration resulting from increased capillary permeability with consequent loss of plasma, especially into the damaged area.[14, 43, 60-63, 137, 138, 256, 269,435, 613] As mentioned above, the extremely sensitive endothelial cells of the capillaries readily become permeable under the influence of damage, but shock ensues even if the resulting hemoconcentration is prevented by transfusion or—as in shock due to hemorrhage—if no hemoconcentration occurs. Furthermore, not every type of increased capillary permeability leads to shock. This theory also fails to explain what makes the capillaries permeable in cases of spinal, muscular exercise, or psychic shock in which there is no direct interference with the endothelial cells.

3. The Theory of Endogenous Intoxication: Most workers believe that toxic metabolites which are released from the damaged tissues into the blood

stream are the mediators between the injured area and the rest of the body. In the light of the alarm reaction concept, it becomes evident that, even if we accept this, there must be a second mediator which causes the tissues to release a toxic metabolite, since not only direct injury to tissues (burns, trauma, etc.), but also any intervention necessitating adaptation (nervous lesions, cold, muscular exercise, etc.) elicits an alarm reaction with an initial shock phase. It is probable that this link in the chain of events is not always the same; in the case of nervous shock it may be a nervous stimulus, in decreased oxygen tension it may be the anoxia, and in cases of toxic shock it may be the injected poison itself which causes the cells to release shock-producing metabolites.

Among the hypothetical shock-producing metabolites, *histamine* has received particular attention ever since Abel and Kubota[1] expressed the view that its liberation from traumatized tissues is the fundamental cause of wound shock. Many investigators have discussed this theory as a possible interpretation of shock caused by trauma,[14, 35, 36, 86, 122, 124, 277, 300, 531, 610, 652] burns,[34, 45, 192, 216, 217, 255, 277, 447, 688] cold,[281, 608] peptone,[123, 192, 194, 260] snake venoms,[179, 180, 192, 193, 322, 323] bee venom,[192] microbial toxins,[192, 324] intestinal occlusion,[8] allergy,[684a, 684b] and numerous other damaging agents.[493, 647, 696] Although Rose and Browne[510] found a decrease in blood histamine during shock, others[387, 651] expressed the opinion that in the final analysis, histamine liberation from the tissues may be the basic cause of the alarm reaction syndrome, irrespective of the evocative agent. The writer[545, 550] also considered this possibility but emphasized that there is no irrefutable evidence to support it and that numerous other metabolites might be invoked with almost equal justification. Among these metabolites are *adenosin derivatives*,[697] acetylcholine,[545] the *"Frühgift"* of Freund,[215] the *leucotaxin* and *necrosin* of Menkin,[424a] and *vasoconstrictor substances*.[468, 469]

Kendall and Ingle[325] rejected the histamine theory of the alarm reaction, favoring the concept that *potassium* may be the shock-producing metabolite, since as they say: "In all the conditions given by Selye as suitable to produce the 'alarm reaction,' there is a rise in the concentration of potassium in the serum." It is possible, however, to raise serum potassium without eliciting an alarm reaction, and animals which developed hypopotassemia due to desoxycorticosterone overdosage are especially prone to develop the shock phase.[539]

Various more or less exactly defined *other toxic metabolites* have been considered,[24a, 55, 66, 212, 239a, 273, 317, 385, 419, 428, 440a, 631, 638, 688] but none of these theories have received sufficient support to be acceptable.

The possibility of *enterogenic intoxication* should also be kept in mind in certain cases, since owing to gastrointestinal ulcer formation toxic substances are readily absorbed from the gut during the alarm reaction.[553] It is interesting in this connection that the anoxia at high altitude is claimed to increase the permeability of the gastrointestinal tract, thus predisposing to food allergy.[30a] It must be remembered, however, that shock can also develop in eviscerated animals.

4. The Theory of Nervous Disturbance: The possibility that nervous factors may play a role in eliciting the symptoms of the shock phase[116, 273] has

briefly been discussed above in the sections on "Collapse" and "Factors Influencing the Course of the General Adaptation Syndrome" (e.g., spinal cord transection, severance of the pituitary stalk, etc.).

There is some evidence which would suggest that many if not all the manifestations of the general adaptation syndrome are due to *conditioned reflexes.* Thus, it was found that the tachycardia elicited by adrenalin in the dog can subsequently be produced even by the injection of saline solution when a conditioned reflex to injection has already been established.[626] Although this example is somewhat far fetched, the fact remains that certain manifestations of the general adaptation syndrome, which are dependent upon pretreatment or training, could be based upon the development of conditioned reflexes.

It has also been claimed, with more or less justification, that the *vegetative nervous system* may play a prominent role, namely that an overstimulation of the sympathetic division could be the cause of shock.[208, 640, 641] This did not remain uncontested.[198] Yet, perhaps certain manifestations of the alarm reaction may be selectively mediated by nerves. Thus, it is claimed that vagotomy, adrenal denervation, and spinal cord transection exert a pronounced effect on the glycemic response to alarming stimuli.[225-227] It is well known, furthermore, that sympathectomy interferes with many adaptive reactions and prevents adrenalin liberation in emergencies.[90a]

The fact that strong *nervous stimuli can act as alarming agents* (e.g., rage, spinal cord transection) has repeatedly been mentioned in the course of this review and hardly requires much further discussion. Shock caused by intestinal obstruction has often been considered to depend largely upon nervous irritation.[198, 270, 632] It was found, however, that preliminary exclusion of the extrinsic nerve supply of the gastrointestinal tract does not influence the survival time of cats in which shock was produced by obstruction of the intestines.[198]

Fear has also been regarded as a possible causative factor in shock, by increasing the output of adrenalin and producing vasoconstriction with increased capillary permeability, hemoconcentration, and secondary fall of blood pressure.[88, 208, 210] Neurogenic shock has been produced by carotid sinus stimulation (even in the anesthetized dog) but this probably has little bearing upon shock in man since similar conditions would hardly arise.[477] Experiments planned to prove that *anesthesia alleviates shock* have yielded very contradictory results, probably because deep anesthesia in itself can be an alarming stimulus.[63] To make anesthesia a useful shock-preventing agent, care must be taken that its own alarming effect be less pronounced than that of the nervous stimulus which it is supposed to counteract.[381, 438, 492, 539]

5. The Theory of Disturbed Thermoregulation: It is a well-known fact that in severe shock the mechanism of thermoregulation is disturbed and the body temperature falls. Furthermore, exposure to excessive cold can produce shocklike symptoms by depressing the body temperature.[545] It is true that the alarm reaction symptoms produced by transection of the spinal cord can to some extent be prevented by maintaining the body temperature.[126, 127] However, exposure to excessive heat may also lead to shocklike symptoms although the

body temperature rises,[542] and it is common clinical experience that, in patients suffering from trauma or burns, shock is not necessarily prevented by maintaining the body temperature on a normal level.

6. The Theory of Hypochloremia: The *hypochloremia,* which many investigators regard as characteristic of shock, is absent when muscular exercise is the evocative agent.[557, 563] This is particularly true of the reputedly typical decrease in red cell chlorides.[312, 313] Furthermore, marked hypochloremia may be elicited (e.g., by desoxycorticosterone overdosage) without any shock symptoms.

7. The Theory of "Leucopoietic Substances": Among the individual manifestations of the alarm reaction, the leucocytosis has received particular attention. Numerous investigators expressed the view that metabolites, liberated during the shock phase, stimulate leucocyte formation, since at this time the blood acquires the property of increasing the leucocyte count in normal animals.[81-83, 92, 139, 446] Such leucocytosis-producing metabolites have been termed "*neutrophillins,*"[18-23, 275, 444] *leucotaxin,*[424a] or "*leucopoietins.*"[40] Other investigators postulate the existence of a special *leucocyte center* in the brain.[64, 260, 278, 449, 511-513, 522, 653]

Beer[40] united these two theories by assuming that the leucocytosis is produced through stimuli exciting the leucocyte center which, in turn, causes liberation of leucopoietic substances. On the other hand, Feenders[191] was unable to demonstrate any leucopoietic effect with the blood of animals taken at the peak of the leucopoietic reaction. Investigations attempting to determine whether transection of the spinal cord, splenectomy, or thyroidectomy prevents the leucocytic reaction yielded contradictory results.[20, 22, 23, 275, 452, 471]

Blockade of the reticulo-endothelial system does not interfere with the effect of the alarm reaction on the white cell count.[186, 188]

The recent discovery that corticotropic anterior lobe extracts and corticoid adrenal hormones have a pronounced effect upon the white cell picture during the general adaptation syndrome will be discussed in connection with the endocrine theories.

8. The Deficiency Theory: In discussing the many previous theoretical interpretations of the shock phase, we have pointed out that they may explain certain instances of shock, but there are other types which cannot be interpreted by them. This led us to consider the possibility that shock may not always be caused by the same mechanism. It is true that much weighty evidence has been brought forward in favor of one or the other formulation of the intoxication theory, but it is perhaps profitable also to consider the possibility that shock symptoms may be caused by deficiency in certain metabolites rather than by the presence of excessive amounts of them. All the classical experimental arrangements, quoted to prove the toxic theory, are equally applicable to the deficiency theory. For instance, the fact that shock following occlusion of a vascular territory by a tourniquet occurs only after re-establishment of the circulation can equally well be interpreted as due to intoxication of the organism by metabolites which come from the damaged tissue or by loss of vitally-important substances from the general circulation into the area of damage.

In some instances, it is indubitably a deficiency that causes shocklike symptoms. Thus, we have been able to produce typical shock by partial hepatectomy,[584] a condition in which no tissue remaining in the body is directly lesioned nor is there any damaging substance introduced into the organism. In this instance, just as in the case of shock due to anoxemia or hypoglycemia, it is the lack of something rather than an excess of toxic metabolites that was the primary cause of shock and cellular injury, although secondarily this lack may have led to the formation of toxic substances. It is conceivable that lack of certain substances necessary for shock defense plays a part in many if not all types of shock. The interpretation of the shock phase as one of "relative adrenal insufficiency"[502, 545, 587] is essentially one application of this deficiency theory.

The previously quoted experiments,[151, 585] showing that much blood sugar disappears during circulation through a traumatized limb, might also be interpreted on the basis of the deficiency theory. Increased glucose combustion in the damaged tissue would probably require the presence of large quantities of substances (e.g., coenzymes), which are necessary for glucose utilization and by attracting these into the area of damage, the body may become deficient in them.

Attention should also be called to the fact that, among the previously mentioned interpretations, the theory of hypochloremia and the theory of dehydration also represent modified types of the deficiency theory. Incidentally, there is no proof that it is actually water loss into the damaged tissues that is of importance. Compression treatment of crush injuries of limbs has proved quite effective in clinical and experimental medicine and this cannot always be entirely attributed to the prevention of water loss into the damaged tissue. The possibility that other important blood constituents are lost into the tissues has likewise been considered.[316, 472]

9. Other Theories of Shock: Among the numerous other theories proposed to explain shock, suffice it to mention those of *acapnia,*[265, 267] *fat embolism,*[59, 246, 484, 485, 664] *acidosis,*[249, 250, 333, 389, 418] and *constriction of the hepatic vessels.*[416] More recently,[185] it has been suggested that, at least in cases of shock caused by burns, *cardiac lesions* are responsible for the general damage. However, none of these latter theories have received much support.

B. Theories Concerning the Entire General Adaptation Syndrome.—

1. The Hypothesis of Adaptation Energy: The observation that resistance is increased during the countershock phase of the alarm reaction intimated that the "adaptability" of the organism is mobilized in some way. On the other hand, following prolonged treatment with an alarming stimulus, that is, during the "resistant stage" of the general adaptation syndrome, when the organism has acquired a high degree of adaptation to the agent to which it had been exposed, it becomes especially irresistant and unable to adapt itself to other damaging agents. This seemed to signify that the body possesses only a limited amount of "adaptability" or "adaptation energy" which is consumed while the adaptation is acquired to a certain agent, so that less of it is available for resistance against other agents. This concept is also supported by the ob-

servation that continued treatment with the same agent (which originally caused an alarm reaction and to which the organism later became adapted) eventually becomes damaging again ("stage of exhaustion" of the general adaptation syndrome). It would be extremely difficult to explain the loss of an already acquired adaptation without assuming that, due to continued use, all the available adaptation energy of the organism had been exhausted.[231, 427, 556, 558-560, 568] The extensive and painstaking studies of Sundstroem and Michaels[629] on adaptation to anoxia lead them—quite independently—to a concept very similar to ours. They also found that adaptation proceeds in three stages: (1) "preadaptive," (2) "adapted," and (3) "postadapted," that it depends upon a defensive hyperactivity of the adrenal cortex, and that it terminates in a final breakdown reminiscent of cortical insufficiency. It is likewise worth mentioning in this connection that Gause's[222] studies concerning the relation of adaptability to adaptation led him to conclude that "the stronger the initial inherent adaptation, the weaker is the adaptability, and vice versa. This conclusion follows from observations on unicellular organisms, but it was shown to agree well with the data obtained in the work with other animals."

To quote but one possible application of this hypothesis to contemporary clinical medicine, we may call attention to the fact that aviators, who had to adapt themselves to work under nervous tension at a high altitude, often break down following a period of apparently complete inurement. The period of breakdown is characterized, among other things, by gastrointestinal disturbances and other manifestations reminiscent of the "stage of exhaustion" of the general adaptation syndrome. In such cases, it has been customary to speak of exhaustion of the "nervous energy reserve."[663]

Of course, it must be admitted that the adaptation energy hypothesis does not even attempt to explain the pathogenic mechanism responsible for the development of the various manifestations of the general adaptation syndrome. It is offered merely as a working hypothesis which may help to visualize the fact that adaptation to a multiplicity of agents occurs in three distinct stages.

2. Theories Concerning the Functional (Mainly Hormonal) Interrelations During the General Adaptation Syndrome: The functional interrelations, between the various organs affected by the general adaptation syndrome, are still far from being clearly understood. It has long been suspected, however, that hormones play an important role in adaptive processes[4a, 163a, 390a, 522a] and considerable progress has been made along these lines since the first publication on the alarm reaction appeared nearly ten years ago. It would be premature to outline a hypothesis attempting to interpret all manifestations of the adaptation syndrome. There is practically no information as yet concerning certain links in the chain of events, but some interrelations have been proved beyond doubt and others have at least been made extremely probable by experimentation. At this stage it is best not to lean too heavily upon any preconceived theoretical concept, but as a working hypothesis it may be useful to outline those correlations which are in best accord with the facts observed. (For a more detailed description of the observations cited in support of our hypothesis, the reader is referred to the previous sections of this review.)

It must be admitted, at the outset, that we do not know as yet through what pathways nonspecific damage evokes the clinical manifestations of "shock." Loss of body weight (due at least partly to increased protein catabolism and tissue destruction), the formation of gastrointestinal ulcers, a temporary rise in plasma potassium, and a temporary fall in plasma chloride as well as other purely *retrogressive or catabolic manifestations* (disturbance of thermoregulation, blood circulation, etc.) are all characteristic of the "shock phase." The various theories which attempt to explain how a comparatively localized injury can influence the entire body and produce all these changes during shock (intoxication, deficiency, etc.) have been discussed in the previous section. We do not feel that any of these theories are adequately proved, and hence we shall not dwell any longer on the possible pathways through which nonspecific damaging agents might elicit the shock syndrome. It is of great theoretical importance, however, to keep in mind that, whatever this pathway might be, it does not require the integrity of the hypophyseo-adrenal system. It will be remembered that all these destructive, or detrimental, changes of the shock phase can be elicited in hypophysectomized or adrenalectomized animals and indeed tend to be much more severe in the absence of either or both of these glands. This is noteworthy because a series of other changes characteristic of the general adaptation syndrome—especially those which presumably are of a defensive nature—depend upon the integrity of the hypophysis and the adrenal cortex.

The *hypophysis* probably occupies the most important, central position in the constructive or defense reactions which are essential for resistance and adaptation to nonspecific damage. There is good evidence to show that under such influences, the hypophysis produces increased amounts of *corticotropic hormones* since in hypophysectomized animals, the adrenal cortex shows signs of hypertrophy or increased functional activity (the apparently exceptional behavior of birds has been mentioned above).[545] We have considered the possibility that any type of alarming stimulus may cause a condition of "relative adrenal cortical insufficiency" and that the increased corticotropic hormone production might be viewed as a type of compensatory hypertrophy such as that seen after partial adrenalectomy.[545] Other investigators[522c, 634] essentially concur with this view. Our interpretation received additional support from the many observations showing that, in animals overdosed with corticoids, the response of the adrenal cortex to alarming stimuli is subnormal, presumably because of deficient corticotropic hormone production.

It has been claimed that during the alarm reaction an excess of corticotropic hormone can actually be demonstrated in the blood[651]; however, because of the unusual bio-assay method employed, this work requires confirmation.

Teleologically speaking, increased corticotropic hormone production is a useful reaction to stress since it augments the corticoid hormone production of the adrenals and thus raises nonspecific resistance.

On the other hand, while the pituitary is actively engaged in increased corticotropic hormone production it is apparently less capable of elaborating *growth hormone, prolactin,* and *gonadotropic hormones* ("shift in hormone pro-

duction''),[269a, 582] hence, during the general adaptation syndrome, somatic growth, milk secretion (in lactating animals), and the development of the gonads are inhibited. In the male there is an involution of the spermatogenic epithelium and of the Leydig cells with a consequent atrophy of the accessory sex organs (due to decreased testoid hormone production). In the female there are abnormalities in the development of the follicles and corpora lutea which may lead to disturbances in the sexual cycle (amenstrual ovulation, anovular menstruation, etc.).

There is ample evidence (see section on Pathologic Anatomy) that the *adrenal* cortex is enlarged and shows histologic signs of increased activity, especially during the alarm reaction phase of the general adaptation syndrome. During the stage of resistance, these changes become less obvious; during the stage of exhaustion there is a second period of marked adrenal enlargement which may or may not be accompanied by an overproduction of corticoid substances.

There can hardly be any doubt that at least during, and immediately after the alarm reaction stage, the enlargement of the adrenal is accompanied by a pronounced increase in *corticoid hormone* production. It was found that, in patients, following operations, burns, and other types of exposure to alarming stimuli, the corticoid activity of the urine rises considerably above normal.[77, 232, 656, 657, 673, 674] It has been claimed also that the increased diuresis noted in aviators at high altitude may be the result of increased cortical hormone secretion, since the corticoids are known to have diuretic properties.[479] It should be pointed out, however, that this interpretation has not been proved as yet.

The adrenal cortex is also a site of *17-ketosteroid and testoid hormone* production and hence it appeared of some interest to establish whether this function of the cortical cells is also influenced by alarming stimuli. In general it may be said that most relevant investigations are in accord with the assumption that immediately following exposure to an alarming stimulus, the 17-ketosteroid and testoid excretion in the urine rises for a brief period and then declines to subnormal levels.[113, 204-206, 213, 287, 623] These observations suggest that under the immediate influence of an alarming agent perhaps the 17-ketosteroid and testoid compounds present in the adrenal cortex are eliminated with the corticoids, but later, during the stage of resistance, the adrenal cortex produces only, or at least predominantly, corticoid compounds (''shift in hormone production''). For this reason, and since the gonads become inactive (lack of gonadotropic hormone secretion), it is understandable that the 17-ketosteroid and testoid production and elimination is subnormal during the later stages of the general adaptation syndrome.

Albert[7] examined the possible testoid and folliculoid hormone production by the adrenals during the alarm reaction. He found that ''in gonadectomized animals treated with 10% formalin solution there occurred a marked hypertrophy of the adrenal glands but no significant change in the size of the accessory sex organs (vaginal smears and preputial glands in the female; seminal vesicles

and prostate in the male).'' From this he concluded ''that the adrenal cortical hypertrophy, so characteristic of the alarm reaction, is not accompanied by increased sex hormone production.''

It is known that certain pituitary corticotropic preparations can selectively stimulate the testoid production of the adrenal cortex and that the production of sugar-active and salt-active corticoids is not always proportionate. Hence, it appears very probable that there are three different corticotropic principles which stimulate the testoid, salt-active corticoid, and sugar-active corticoid hormone production of the adrenal, respectively.[576] Apparently during the general adaptation syndrome only the production of the latter two is increased.

It has often been argued that if resistance during the alarm reaction were really dependent to any great extent upon increased corticoid hormone production, the treatment of shocklike conditions with corticoids should give more satisfactory results than have so far been obtained. In this connection it is of interest to note that even the basic corticoid hormone production of the adrenal is apparently enormous in comparison with the amount of corticoid substance that has usually been administered for therapeutic purposes. Thus, bio-assays performed on the venous blood of adrenals indicate that ''the average output of one suprarenal gland, per min., per kg. body weight, was equivalent to 0.6 g. of suprarenal tissue'' . . . ''the potency of 1 ml. suprarenal plasma was at least several times, occasionally 10-12 times, as high as the activity obtained by extraction of 1 g. of gland.''[659] There is very convincing evidence that, in combatting damage during the alarm reaction, the sugar-active corticoids are much more effective than the salt-active corticoids.[583, 587] Indeed, there is some doubt whether salt-active corticoids are of any value except in very special cases (potassium chloride intoxication, dehydration, etc.). Since commercial preparations of sugar-active corticoids are often impure and since they are not as yet readily available, it is not surprising that, up to the present, it has rarely been possible to improve markedly upon the natural performance of the adrenal cortex.

It is noteworthy that the increased production of corticoids is especially important during the alarm reaction phase of the general adaptation syndrome. Adrenalectomized animals need much larger than maintenance doses of corticoids to withstand sudden stress (anoxia, muscular exercise, cold),[601] but, after adaptation to a damaging agent, they usually tolerate it on maintenance doses of corticoids.[351, 548, 551, 659]

Nonadapted, adrenalectomized animals fail to develop a normal countershock phase, and hence it has been concluded that corticoids play an important role in the development of countershock phenomena. Some recovery from the shock phase is seen even in adrenalectomized animals if the alarm reaction is not too severe. It is noteworthy, however, that in the case of chronic exposure even to mild stress, adrenalectomized animals can maintain themselves in the stage of resistance only for a very short period before exhaustion and death supervene. Hence, it must be concluded that, although corticoids facilitate the

process of adaptation and delay the onset of exhaustion, they are not entirely indispensable for inurement.[548, 551, 554]

The *chromaffin system* has been shown to play a prominent role only during the first few minutes of the alarm reaction when the blood pressure and the blood sugar show their transitory rise. It is questionable whether it is of great importance at any other time during the course of the general adaptation syndrome. It has been claimed that the discharge of chromaffin granules which occurs during the shock phase may be secondary to dehydration, since it can sometimes be prevented by maintaining the blood volume with infusions.[209, 211] Animal experiments indicate that shock is not connected either with exhaustion[491] or with excess activity[487] of the sympathin and adrenalin-producing system.

The excess corticoid hormones (produced by the adrenal cortex, under the influence of corticotropic hormones) cause a number of secondary changes, especially in the lymphatic organs, the antibody titer, carbohydrate metabolism, electrolyte metabolism, the cardiovascular system, and the kidney, which can now be considered individually.

The *thymus* and *lymphatic organs* involute under the influence of alarming stimuli in the intact animal, but this involution is inhibited by adrenalectomy or hypophysectomy.[542, 545] The thymus involution caused by corticotropic pituitary extracts is directly related to the adrenal enlargement,[459] and corticotropic extracts which cause marked thymus and lymph node involution in the intact or hypophysectomized animal have no such effect following adrenalectomy.[611] On the other hand, corticoids induce thymus and lymph node involution even in hypophysectomized or adrenalectomized animals, and hence it is reasonable to assume that their action is not mediated through the hypophysis or adrenal cortex.

It may be mentioned incidentally that some workers hoped to clarify the role of the thymus in the alarm reaction by examining the effect of thymectomy upon the survival of adrenalectomized rats but these investigations yielded no positive data.[538]

The transitory *lymphopenia and polymorphonuclear leucocytosis,* characteristic of the alarm reaction, have been reproduced in experimental animals by purified corticotropic pituitary extracts.[497] The latter also depress the lymphocyte count in thoracic duct lymph.[497a] On the other hand, the changes in the white cell count induced by alarming stimuli are not as constantly and characteristically inhibited by adrenalectomy as is the involution of the thymus and of the other lymphatic organs.[130] It is somewhat uncertain, therefore, whether the circulating leucocytes are as strictly under adrenal control as the thymocytes.

Recently, several interesting facts came to light which indicate that the alarm reaction may also have an important influence upon *serologic immune reactions.* It has been found that lymphocytes of normal rabbits contain a globulin identical with the normal serum γ-globulin which is important for antibody formation.[681] Furthermore, "labelled globulin" (antibody protein) has been demonstrated in lymphocytes isolated from the lymphoid tissue of immunized

mice.[154] The presence of immune bodies in lymphocytes has also been confirmed in the immunized rabbit.[257] All these observations suggest that the lymphatic organs play an important role in immune reactions. It has been noted, furthermore, that corticotropic hormone secretion accelerates the rate of release of antibodies from the lymphoid tissue of immunized rabbits[157] and that alarming stimuli enhance the antibody titer in the sera of previously immunized animals.[92] Finally, it is claimed that the enhancement of antibody titer, produced by alarming stimuli, can also be elicited by corticotropic pituitary extracts and adrenal cortical extracts, but not by desoxycorticosterone acetate. Cortical extracts, but not corticotropic extracts, are effective in this respect, even in the adrenalectomized animals. From these experiments it was concluded that "adrenal cortical mediation is essential for the control of the release of antibody from lymphocytes."[155]

The afore-mentioned investigations make it very probable that the general adaptation syndrome influences serologic immunity. This may shed some light upon the observation that during the countershock phase of the alarm reaction anaphylactic phenomena are inhibited.[310, 311]

The theoretical interpretation of the changes in *carbohydrate metabolism,* which occur during the general adaptation syndrome, has already been discussed in the section "Metabolic Changes." Suffice it to recall here, first, that the changes in carbohydrate metabolism elicited by certain alarming stimuli (anoxia, folliculoids) and by corticotropic anterior pituitary extracts are inhibited by adrenalectomy; second, that the sugar-active corticoids [e.g., corticosterone, dehydrocorticosterone, but not the salt-active corticoids (desoxycorticosterone*)] exert a pronounced effect upon carbohydrate metabolism; and, third, that animals whose adrenal cortex is inactivated by hypophysectomy, adrenalectomy, or "compensatory atrophy" (due to prolonged desoxycorticosterone overdosage) exhibit a great tendency to develop fatal hypoglycemia under the influence of alarming stimuli. All these observations suggest that the need for sugar is increased during the alarm reaction and hence an increased secretion of sugar-active corticoids is essential for resistance to stress. This increased sugar-active corticoid production may lead to hyperglycemia, increased glycogen deposition in tissues, and occasionally even to glycosuria if experimental conditions are such that sugar utilization is impeded (anoxia, thyroidectomy?). It is not impossible that certain types of clinical diabetes—especially those in which continued stress and strain appear to play a role—may have their origin in this type of hormonal derangement rather than in a primary pancreatic failure.

The prominent changes in *electrolyte metabolism,* seen during the general adaptation syndrome, have also been discussed in the section "Metabolic Changes." In clinical shock, hypochloremia and a rise in plasma potassium are outstanding. These are reminiscent of the hypochloremia and potassemia of

*In all our experiments, discussed in this review, desoxycorticosterone was administered in the form of its acetate.

adrenal insufficiency and were partly responsible for the interpretation of the shock phase as a type of "relative adrenal cortical insufficiency."

It is known that overdosage with salt-active corticoids (e.g., desoxycorticosterone) causes sodium retention accompanied by hypochloremia and hypopotassemia. It has been claimed that the cardiovascular and renal changes produced by chronic overdosage with desoxycorticosterone are secondary to the hypopotassemia induced by this compound.[134, 135, 159] We disagree with this view since in our experience the maintenance of normal blood potassium levels through oral administration of excess potassium chloride failed to prevent these lesions in animals receiving excessive amounts of desoxycorticosterone.[407, 599] It appears more probable that the salt-active corticoids produce organ changes by virtue of their sodium retaining property. This interpretation is supported by the observation that animals kept on a high sodium chloride intake are particularly sensitive to the toxic effects of desoxycorticosterone.[599, 602] On the other hand, the so-called "acidifying salts" (ammonium sulfate, ammonium chloride, ammonium nitrate, and calcium chloride) protect against this steroid,[595, 599] and the possibility has been considered that this may be due to their ability to bind sodium and facilitate its excretion. Interestingly, the life-maintaining action (tested on adrenalectomized rats) of desoxycorticosterone is not significantly influenced by ammonium chloride.[603]

For the understanding of the hormonal interrelations during the general adaptation syndrome, it is of fundamental importance to elucidate through what mechanism overdosage with salt-active corticoids produces organ changes. It will be recalled that desoxycorticosterone (especially when given to animals on a high sodium diet) produces *vascular lesions* identical with those seen in periarteritis nodosa,[581, 593, 600] *hypertension*,[577, 593] *myocardial*[592] and *joint lesions* similar to those observed in acute rheumatic fever,[605] *nephrosclerosis*,[572, 577, 591-593] and sometimes acute *nephritis*.[539] It was obvious to consider the possibility that the diseases of man which are thus imitated by desoxycorticosterone overdosage might arise as a result of an excessive production of endogenous salt-active *corticoids*. In this sense, these lesions would have to be interpreted as "diseases of adaptation."

There is a good deal of evidence in favor of this interpretation, inasmuch as the afore-mentioned diseases have long been known to occur following sudden or chronic exposure to stress (infections, cold, nervous strain, etc.). All these are conditions which elicit the adaptation syndrome and increase corticoid hormone production. It is not inconceivable, therefore, that the defensive production of corticoids—while useful in raising the resistance of the body to stress—have certain detrimental side effects due to the inherent toxicity of the corticoids. Such a defense reaction which, at least partly, defeats its own purpose, is not without precedent in experimental pathology. It is known that certain essentially useful immunologic defense reactions are responsible for serum sickness and anaphylaxis, both of which conditions are definitely detrimental. Even in endocrinology we have examples of defense reactions which elicit harmful

side effects. Thus, in the case of renal disease, the blood phosphate may rise to dangerous levels, and, in order to compensate for this, the parathyroids produce an excess of parathyroid hormone through which the blood phosphate level is restored toward normal. This is obviously a useful defense reaction, but its consequence is that, under the influence of excessive endogenous parathyroid hormone osteitis, fibrosa-like changes develop in the skeleton and "renal rickets" results. It is possible that the diseases of adaptation are the consequences of a similar derailed or excessive adaptive reaction on the part of the adrenal cortex which under certain conditions of strain may produce disproportionate and excessive amounts of salt-active corticoids.

Subsequent work showed that overdosage with crude *anterior lobe extracts* can produce the same organ lesions as desoxycorticosterone[576] and the changes produced by these extracts are likewise most readily obtained in animals receiving a high sodium chloride intake and are effectively inhibited by the administration of acidifying salts (e.g., ammonium chloride).[251] Therefore, it is possible that the anterior lobe extract acts through its corticotropic hormones upon the adrenal and causes it to release an excessive amount of salt-active corticoids. These, in turn, would produce the same overdosage symptoms as are elicited by injection of desoxycorticosterone itself.

Notably, however, desoxycorticosterone administered to hypophysectomized animals fails to depress the blood chlorides[579] and causes little or no morphologic lesions in the cardiovascular system, the kidney, or the joints[594] This observation raises the possibility that a hypophyseal principle may be produce the "diseases of adaptation" directly and not through the intermediary of the adrenal cortex. It is indeed not inconceivable that even desoxycorticosterone acts only through the intermediary of the pituitary rather than vice versa. Yet, preliminary experiments[590] indicate that, in adrenalectomized animals (kept on maintenance doses of adrenal cortical extract), hypophyseal preparations do not elicit the usual organ changes.

However, in connection with experiments on hypophysectomized or adrenalectomized animals, it must be kept in mind that it is difficult to maintain these on diets high in sodium and protein but low in carbohydrate content. On the other hand—as mentioned above—high carbohydrate diets in themselves suffice to give protection against the production of cardiovascular and renal changes by either desoxycorticosterone or anterior pituitary preparations. Hence, it is difficult to form a definite opinion concerning the causative hormonal mechanism and it must be admitted that the morphologic changes characteristic of overdosage with either desoxycorticosterone or anterior lobe extracts may be due to any of the following endocrine interactions: (1) Both desoxycorticosterone and anterior lobe extracts may act upon the target organs (cardiovascular system, kidney, etc.) directly and independently of each other. (2) The anterior lobe preparation may, through adrenotropic hormone, cause the adrenal cortex to produce desoxycorticosterone-like substances, which alone would have a direct action upon the target organs. (3) Conversely, desoxy-

corticosterone may act upon the pituitary and cause it to secrete a substance directly affecting the target organs involved. (4) Both anterior pituitary and adrenal corticoid hormones may have to act simultaneously upon the target organs, the lesions produced in the latter being the result of a synergistic action between corticoids and anterior lobe hormones.

Among these various possibilities, the second is, a priori, most probable since there are many other examples proving the common occurrence of this type of mechanism. Thus, the thymus atrophy in the alarm reaction is proved to result from the liberation by the pituitary of adrenotropic hormone, which

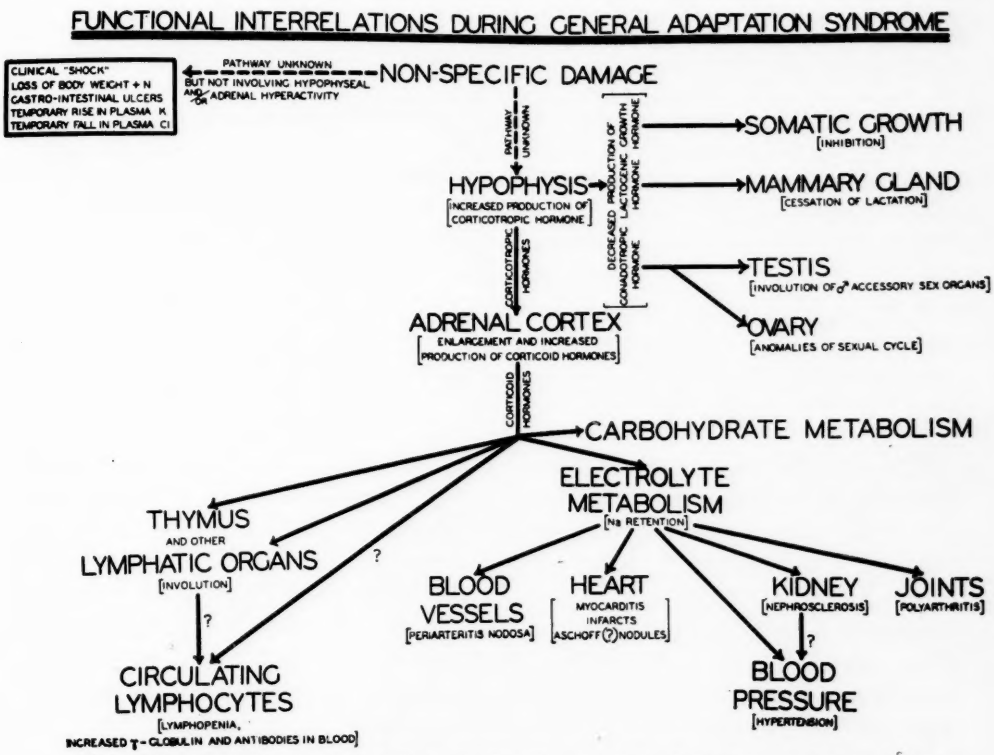


Plate XX.—Functional interrelations during the general adaptation syndrome. Shematized drawing indicating that nonspecific damage causes clinical shock, loss of body weight and nitrogen, gastrointestinal ulcers, and temporary rise in plasma potassium with fall in plasma chlorine through unknown pathways (nervous stimulus?, deficiency?, toxic metabolites?) but manifestly not through the stimulation of the hypophyseo-adrenal mechansim. This is proved by the fact that the above manifestations are not prevented either by hypophysectomy or by adrenalectomy; they even tend to be more severe in the absence of either or both of these glands.

Nonspecific damage, again through unknown pathways, also acts upon the hypophysis and causes it to increase corticotropic hormone production at the expense of a decreased elaboration of gonadotropic, lactogenic, and growth hormones. The resulting corticotropic hormone, excess causes enlargement of the adrenal cortex with signs of increased corticoid hormone production. These corticoids in turn cause changes in the carbohydrate (sugar-active corticoids) and electrolyte metabolism (salt-active corticoids) as well as atrophy of the thymus and the other lymphatic organs. It is probable that the cardiovascular, renal, blood pressure, and arthritic changes are secondary to the disturbances in electrolyte metabolism since their production and prevention are largely dependent upon the salt intake. The changes in γ globulin, on the other hand, appear to be secondary to the effect of corticoids upon the thymicolymphatic apparatus.

We do not know, as yet, whether the hypertension is secondary to the nephrosclerosis or a direct result of the disturbance in electrolyte metabolism caused by the corticoids. Similarly, it is not quite clear, as yet, whether corticoids destroy the circulating lymphocytes directly or influence the lymphocyte count merely by diminishing lymphocyte formation in the lymphatic organs. Probably both these mechanisms are operative.

in turn causes the adrenal cortex to secrete thymus involution-producing corticoids. Similarly, the nervous stimulus of copulation causes progestational transformation in the endometrium because it stimulates the pituitary to secrete an excess of gonadotropic hormones, which in turn act upon the endometrium through the corpus luteum hormone.

Be this as it may, the production of the "diseases of adaptation" with hypophyseal extracts furnished additional proof against the theory that these diseases are secondary to the depression of blood potassium occasioned by the salt-active corticoids, as our hypophyseal preparations did not depress the blood potassium and yet produced the typical organ lesions. These experiments are in accord, however, with the view that sodium retention plays a role in the pathogenesis of these lesions, since administration of excess sodium chloride facilitates their production both by pituitary and by corticoid preparations.

The possibility that the *thyroid* may play an important part in the development of the diseases of adaptation must be considered also. The fact that hypophysectomy inhibits the nephrosclerotic (and allied) actions of desoxycorticosterone could, at least partly, be due to thyroid inactivation, especially since thyroidectomy has a similar effect and the nephrosclerotic potency of anterior pituitary extract is also diminished in the absence of the thyroid gland.[251, 259] Conversely, thyroxin treatment sensitizes the rat to the nephrosclerotic action of both desoxycorticosterone and anterior hypophyseal preparations.[580, 604] All these observations indicate that, although the thyroid is perhaps not indispensable for the production of nephrosclerosis and allied phenomena, its hormone facilitates their development.

No definite interpretation can as yet be offered as regards the pathogenesis of the hypertension seen during the resistance phase of the general adaptation syndrome, but the following theoretical considerations should be kept in mind. Salt-active corticoids and anterior pituitary preparations elicit hypertension accompanied by the same organ changes (in kidney, heart vessels, etc.) as those associated with the rise in blood pressure induced by nonspecific damage. Experimental work has shown, furthermore, that the adrenal cortex plays an essential role in the production of hypertensinogen probably by stimulating its elaboration in the liver. The presence of the adrenals or desoxycorticosterone treatment are indispensable for the maintenance of the normal hypertensinogen level in rats.[219] It is possible that the pituitary and corticoid hormones act upon blood pressure directly through this mechanism and that the renal changes are independent or are secondary to the high blood pressure. The fact that chronic hypertension elicited in rats by other means does not result in similar renal changes[143] speaks against this latter interpretation. It is not impossible, therefore, that the renal changes are primary and that the blood pressure is raised through the intermediary of pressor principles released by the pathologic kidney tissue.

CLINICAL IMPLICATIONS OF THE GENERAL ADAPTATION SYNDROME

Adaptation to our surroundings is one of the most important physiologic reactions in life; one might even go so far as to say that the capacity of adjust-

ment to external stimuli is the most characteristic feature of live matter.[549] It is hardly surprising, therefore, that some of the most important and most frequent diseases of man appear to be diseases of adaptation. There is increasingly more evidence to show that the diseases of adaptation play the same important role in pathology as the general adaptation syndrome in physiology. The observations reported in the previous sections of this review indicate that some of these diseases (e.g., the clinical syndrome of "shock," the gastrointestinal ulcers, etc.) are merely signs of damage due to lack of adaptation, while others (e.g., hypertension, periarteritis nodosa, nephrosclerosis) are the result of abnormal or excessive adaptive reactions to our environment. We called attention to some of the errors which found their way into pharmacology, bacteriology, and other branches of experimental medicine, because of the impression that, if a certain change appears consistently following treatment with a certain agent (a drug, a microbial infection, exposure to abnormal temperatures etc.), this change is specifically—and perhaps even directly—caused by that agent. If, in such instances, further experimental work reveals that a number of agents can elicit the same change, the task of interpreting the observations appears to be insurmountably difficult and confusion ensues.

There are many similar examples in clinical medicine. For instance, such conditions as nephritis, rheumatic fever, or acute gastric ulcer in some instances indubitably occurred as the result of an acute infection, but in other instances they could, with an equal degree of certainty, be traced to an exposure to intense cold, an intoxication, or an emotional stimulus. If we assume that certain lesions are produced by the response of the body to damage as such, rather than to one specific pathogenic agent, the difficulty of interpreting the comparatively uniform response to diverse agents is no longer insuperable.

Perhaps the strongest argument against this type of reasoning is the fact that the same degree of damage or stress does not necessarily always elicit the same response; even lesions which are manifestly not the specific result of one particular pathogenic agent may be more prone to occur following exposure to one or the other type of damage. To give but one example, nephritis may be caused by a variety of microorganisms, by exposure to cold, or by treatment with various drugs, but it is particularly frequent in patients suffering from staphylococcus infection with tonsillitis, scarlet fever, or sepsis. This does not mean that *the* pathogenic agent of nephritis is a staphylococcus in the sense in which *the* pathogenic agent of tuberculosis is the tuberculosis bacillus. It merely means that staphylococcus infection elicits a somatic response which produces especially favorable conditions for the development of nephritis. Furthermore, we have seen that numerous factors can specifically sensitize or desensitize the body to one or the other manifestation of the general adaptation syndrome. Thus, we have seen that sodium chloride sensitizes while ammonium chloride desensitizes the kidney to the nephrosclerotic action of cold; glucose administration desensitizes while exposure to cold sensitizes the gastric mucosa to the ulcer-producing effect of spinal cord transcision. The dissociation of symptoms resulting from

such selective sensitization or desensitization to one particular lesion, helps to show that the same degree of stress or damage does not always result in the same symptomatology.

It would be interesting to survey all the diseases of unknown etiology from this new point of view and to find out whether those among them which apparently can be caused by a variety of agents belong to the category of the diseases of adaptation. Unfortunately, at the present time, we know far too little about the intricate mechanism of the adaptation syndrome to make such a systematic study profitable. It may be of some value, however, to call attention to a few apparently relevant diseases and cite pertinent literature which suggests that they have some relation to the general adaptation syndrome.

Nephrosclerosis and *hypertension* can most probably be regarded as diseases of adaptation when they occur as a result of continuous exposure to stress and strain.[574] As explained earlier, they may be produced through the intermediary of the hypophyseo-adrenal cortical hormone mechanism. This final common pathway could explain that so many different types of strain may lead to the same end result.

The fact that hypertension[676] and angina pectoris[184] may be elicited by purely emotional stimuli in man should also be kept in mind in this connection.

It is noteworthy furthermore that sodium restriction[246a] and high carbohydrate diets[324a] have repeatedly proved of benefit in the spontaneous renal hypertension of man.

The lipid and especially the cholesterol content of the adrenals is usually very high in cases of hypertension and chronic renal disease[63b, 99a, 99b, 195a, 293a, 332c, 333a, 333b, 678]; however, as a rule, the cortex is not markedly enlarged. It is true that some investigators claim to have found hypertrophy and hyperplasia of the adrenal cortex, sometimes with an unusually high incidence of adenomas, in hypertensive patients,[451a, 503a, 513a, 522b] but others state that these are no more frequent in hypertensive than in normotensive patients.[79a, 142a]

It is perhaps significant that the 17-ketosteroid excretion is markedly lower in hypertensive than in normotensive subjects.[79a] This may represent another instance of the previously mentioned "shift" in the hormone production of the adrenal cortex. While this gland produces excessive amounts of corticoids, it may not be able to elaborate the normal quantity of testoids.

It is of interest that in a patient with established hypertension, subsequent development of Addison's disease caused a fall in blood pressure, which remained unchanged by sodium chloride treatment but returned to the original hypertensive level under the influence of desoxycorticosterone. It was concluded that "the adrenal cortex may be important for the development or maintenance of essential hypertension in man."[473a] some workers[632a] even ascribe the hypotensive effect of various toxic substances and infections to an impairment in adrenal cortical function.

The various forms of *nephritis* have always puzzled pathologists because they appear following—and probably as a result of—such diverse, noxious agents

as tonsillitis, colds, scarlet fever, influenza, other infectious diseases, exposure to cold, pregnancy, intoxication with various drugs, and allergic conditions.[369] In experimental medicine, the similarity of the renal lesions produced by a diversity of agents has also been discussed, and Christian[105] ". . . emphasized the non-specificity of lesions observed in the glomerulus of the kidney and offered this non-specificity as an explanation of many similarities in the signs and symptoms of renal disease." Here again the assumption of a common hypophyseo-adrenal defense mechanism against damage would facilitate the understanding of the fact that such diverse stimuli can produce the same renal change.

The etiology of acute *rheumatic fever* has been discussed by pathologists for more than one hundred years. Recently, it has been more and more customary to consider the condition an infectious disease caused by a specific type of microorganism. Yet Lichtwitz[370] introduces his book on rheumatic fever with the sentence "Rheumatic fever is a non-infectious disease." He believes it to be caused by sensitization to antigens, protein in nature, which in most cases are products of microorganisms. However, he is forced to admit that, in the rheumatic individual, reactivation of the process can be brought about not only by the specific antigen but by a variety of nonspecific factors; "thus fatigue, a chill, an adventitious infection, a slight injury, a touch of indigestion, a mental upset, or increased bodily activity may cause the rheumatic to relapse from quiescent into an acute febrile state." In animals cardiovascular lesions of the rheumatic type were produced by "anaphylactic hypersensitivity" to proteins.[499a]

It has been claimed that even rheumatoid arthritis can be elicited by a purely emotional stimulus.[111]

The main problem is again to find the common pathway which could explain the similarity of the lesions produced by such a diversity of agents. Acceptance of the hypophyseo-adrenal theory does not necessitate abandonment of other interpretations. It merely implies that such agents as cold, bacteria, serologic disturbances, etc., have so influenced the hypophyseo-adrenal defense mechanism that an excessive amount of the salt-active corticoid hormones is elaborated whenever an individual is exposed to a particular type of stress and that the rheumatic attack is the result of such a derailed defense mechanism.

Periarteritis nodosa is another condition which has been produced experimentally by overdosage with anterior lobe or corticoid hormones. This vascular lesion frequently occurs in combination with pituitary or adrenal changes[30b, 206a, 372a, 488a] and in patients who previously suffered from rheumatic fever, and it is often accompanied by hypertension. There is evidence, furthermore, that in man periarteritis nodosa can be the consequence of exposure to a variety of nonspecific damaging agents.[600] Even in animal experiments it was possible to reproduce this condition by mere exposure to such nonspecific damage as cold.[574] It is rather likely, therefore, that periarteritis nodosa likewise belongs to the so-called diseases of adaptation.[577]

There probably also are close relations between the so-called focal necrosis of the adrenal cortex, the *Waterhouse-Friderichsen syndrome* and the diseases

of adaptation. It has been emphasized that the focal necrosis of the adrenal cortex often represents "a replica in miniature of the adrenal changes seen in the Waterhouse-Friderichsen syndrome" and that they appear to be caused by such a diversity of etiological factors as infection, toxemia, endocrine factors, and allergy.[431] Since animal experiments showed that exposure to particularly severe types of stress may cause necrotic lesions in the adrenals it appears quite probable that in man changes of this type are also due to an excessive stimulation of the adrenal cortex which results in a final breakdown. This view receives support from observations showing that the cortical lesions in the Waterhouse-Friderichsen syndrome are suggestive of exhaustion, and that corticoid hormones are beneficial in this condition.[486a, 625a]

There is some reason to believe that *eclampsia* may likewise belong to this group of diseases. Thus, Smith and Smith[614] were struck by the similarity of the organ changes noted in experimental animals treated with "menstrual toxin" and those characteristic of the alarm reaction. These authors found, furthermore, that treatment with adrenal cortical extract is beneficial in patients suffering from eclampsia (a condition which they believe to be caused by a similar "toxin"). They concluded, "that the adrenal cortical exhausion may play a part in the alarming rapidity with which clinical manifestations may increase in severity in the pre-eclamptic patient. Up to a certain point, overactivity of the adrenal cortex may combat the 'toxin' as in the first stages of the 'alarm reaction.' . . ." The histologic similarity between the glomerular lesions seen in eclampsia and those reproduced by a variety of other nonspecific agents has been noted also.[105]

Gastrointestinal ulcers, especially the acute gastric erosions and duodenal ulcers (Curling's ulcer), often noted in association with extensive burns, almost certainly also belong to this group of lesions. It is noteworthy that following burns, intestinal ulcerations occur in conjunction with adrenal hemorrhages and with renal changes similar to those produced by acute overdosage with hypophyseal or corticoid hormones.[177] Furthermore, numerous nonspecific damaging agents have been shown to produce gastric ulcers both in animals and in man.[597] Even purely emotional stimulation may result in the formation of peptic ulcers in man.[433, 691] It is almost certain, therefore, that acute gastric ulcers are part of the adaptation syndrome but there is no adequate proof as yet which would permit us to classify chronic gastric ulcers into this category.

It has already been mentioned that *appendicitis*-like changes may be produced in animals by exposure to very acute alarming stimuli.[546] The appendix contains a great deal of lymphatic tissue and, as we have repeatedly stated, the lymphatic organs are particularly sensitive to nonspecific damage because the corticoids liberated during the general adaptation syndrome cause the lymphocytes to disintegrate. This may perhaps also explain the not uncommon development of appendicitis in patients suffering from a variety of contagious diseases.[236]

The acute *tonsillitis* so often noted after exposure to cold following burns, radiation damage, and other types of nonspecific injuries may perhaps also

find its explanation in a similar phenomenon. It is quite conceivable that the lymphatic organs undergo acute involution as a result of a defensive corticoid hormone production and that microorganisms settle secondarily within the damaged lymphatic tissue, because the latter form a particularly favorable medium for microbial development.

Many other lesions bear some resemblance to the diseases of adaptation, but their connections with the latter have not as yet been the subject of special investigation. Among these we may mention the so-called "*postoperative focal necrosis of the arteries,*"[327] the so-called "*diffuse collagen disease,*"[332b] *fibrositis,*[613a] the *fibrinoid necrosis* and periarteritis nodosa-like changes in the vessels and heart muscles of experimental animals treated with serum,[422] the "*shock disease*" which is often epidemic among the snowshoe hare,[240] and perhaps even some of the types of the so-called "*effort syndrome.*"[238, 367, 694]

It remains to be proved whether or not abnormal adaptive processes play a role in the production of metabolic diseases such as *thyrotoxicosis*[421a, 432] or *diabetes mellitus*[371, 615] when they occur following purely emotional stimuli.

In connection with this latter disease, a number of interesting problems come to mind. We noted in our animal experiments with crude anterior pituitary extracts that the healing of the inflammatory reactions around the injection sites was much improved by the same high carbohydrate diets which also antagonized the toxic effects of the pituitary extract upon the kidney and the cardiovascular system. Could it be that, in diabetes, impaired wound healing is due to a failure of carbohydrate utilization by the tissues? In this event, administration of carbohydrates, plus insulin, to diabetics would improve wound healing through that same mechanism which appears to be operative in our experimental rats, namely, by making more glucose available for tissue repair. Could it be, furthermore, that the gradually decreasing incidence of cardiovascular and renal complications in diabetes is due to the now popular treatment with insulin and diets containing adequate amounts of carbohydrates which facilitate glucose utilization? All of these are still unsolved problems but are questions of sufficient practical importance to deserve systematic experimental analysis.

The connections between *Cushing's syndrome* and the adaptation syndrome have been studied in detail by Albright.[10] He emphasized that the excessive production of corticoids as well as the resulting changes in sugar and electrolyte metabolism in Cushing's syndrome are very reminiscent of those seen in the general adaptation syndrome. This is particularly true of those cases in which the serum potassium and chloride levels are below normal.[110, 686] It is significant, furthermore, that Cushing's syndrome is often conducive to nephrosclerosis and hypertension, that is, changes which are experimentally produced by anterior lobe or corticoid hormones. These observations suggest that in Cushing's disease, we have a condition closely related to the diseases of adaptation but differing from the latter in that the hormonal imbalance is the primary cause of disease, not the consequence of adaptation to exogenous damage.

Even certain types of *Simmonds' disease* may be related to the diseases of adaptation. Thus, certain instances of hypopituitarism, developing after preg-

nancy, were ascribed to "exhaustion" of the anterior lobe, due to increased demands during gestation.[167] This relationship is still very problematic, although it must be admitted that increased demands for excess anterior lobe hormone production during stress may, under certain conditions, cause a breakdown of pituitary tissue.

A close relationship between the general adaptation syndrome and *allergy* has often been suspected, especially since the liberation of histamine-like, toxic metabolites has been considered to play an important role in the pathogenesis of both these conditions. The extensive studies of Williams[684a, 684b] led him to the following conclusion: "I have suggested that physical allergy is a perversion of a normal physiologic reaction, the alarm reaction of Selye. Since I have shown that the hormones of the adrenal cortex can relieve the symptoms of physical allergy and these hormones control the permeability of cell membranes and electrolyte and water metabolism, and since intact adrenal function is necessary for the alarm reaction to take place, I feel that good indirect evidence, that physical allergy is an alteration of this normal mechanism, is at hand."

It is evident from what we have said, that some of the diseases mentioned in this section are by no means proved to be diseases of adaptation. They are listed here merely in order to call attention to their possible connections with the general adaptation syndrome. For other disease (e.g., hypertension, nephrosclerosis, periarteritis nodosa), however, we feel that there is strong evidence to show that they are probably due to abnormal adaptive processes. If this theory proves correct, it follows that some of the most common fatal diseases of man are due to a breakdown of the hormonal adaptation mechanism.

Those investigations reported in this review, which were performed by my co-workers and myself were subsidized at first by the Josiah Macy, Jr., Foundation and more recently by the Commonwealth Foundation of New York, to whom we wish to express our deepest gratitude.

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Editorial

Histamine Antagonists in Allergy

For many years sporadic attempts have been made to produce a single method or remedy which will affect anaphylactic or allergic manifestations, regardless of the specific cause. There have been virtually hundreds of such proposed remedies, the more recent and most discussed of them being histamine injections, histaminase, histamine-azo-protein, ethylene disulfonate and amino acids. Essentially all of these proposed procedures have been shown to be either ineffective or impractical.

While some of the above mentioned methods were employed experimentally and clinically, investigative work was in progress in France in an attempt to produce synthetic antihistaminic drugs. Most of these compounds were either not sufficiently active or too toxic for clinical use. The first of these products to offer clinical worth was antergan (N′phenyl-N′benzyl-N-dimethylethylenediamine), and the results of its clinical use began to appear in 1942 in the European medical literature. In 1945 a modification of this product, neoantergan (N-p-methoxybenzyl-N-dimethylamino ethyl a aminopyridine), was announced. Since neoantergan is tolerated better than antergan, it constitutes at present the antihistaminic drug in use in France.

In this country two antihistaminic drugs, benadryl (B-dimethylaminoethyl benzohydryl ether) and pyribenzamine (pyridil-N′-benzyl-N-dimethylethylenediamine) have been recently made available to the general medical profession. The experience with these drugs by a number of investigators experimentally and clinically in the last two or three years shows that these drugs have activities along several lines. Both are histamine antagonists, as determined by inhibition of contraction of the intestinal strip, bronchoconstriction in the guinea pig, and fall in blood pressure in the cat and dog from histamine. Pyribenzamine is capable of protecting against five to seven times as much histamine as comparable doses of benadryl. In anaphylactic shock both drugs are practically equally effective. In man these compounds inhibit histamine and antigen-antibody skin reactions when applied locally. In allergic manifestations both drugs are highly effective in relieving the subjective symptoms and, to a lesser extent, the lesions of urticaria, angioneurotic edema, "serum-sickness" type of reaction from serums, penicillin and sulfonamides, and the itching of atopic dermatitis. The acute sneezing and coryza stages of hay fever are favorably influenced by both drugs, but the congestive nasal obstruction in the later stages of hay fever or in perennial vasomotor rhinitis are relieved to a much lesser extent. In these types of cases pyribenzamine produces a more favorable response. The action of these drugs in asthma is only moderate, and no de-

pendence can be placed on it. The pollen sensitive asthma sufferers who have neglected their desensitization program because of their reliance on these drugs will be greatly disappointed.

The side-effects of the histamine antagonists are becoming increasingly evident with increasing experiences. Benadryl induces a marked soporific effect in a high percentage of patients, many of whom are so sleepy that they cannot carry on their daily activities. Disregard for this particular action and the resulting lack of alertness in the individual may lead to accidents. Pyribenzamine has a similar action, but to a much lesser degree and less frequently. It has, however, other toxic actions. One of the most frequent is an excitatory effect, consisting of nervousness, tremor, tachycardia (often associated with fall in blood pressure), weakness, and insomnia. A peculiar phenomenon not infrequently observed is a combination of sedation and stimulation. The above symptoms may be present and the patient may be sleepy and yet be unable to sleep. Inability to concentrate and mild mental confusion occur at times. Disturbed appetite, gastric discomfort, and abdominal pain may also occur. Some of these symptoms are also produced by benadryl.

The uses, limitations, and dangers of these drugs should be carefully considered. At best these remedies are only palliative. and that function should be emphasized to the patient. Unless this is continually observed great harm will be done by disruption of desensitization programs. These drugs confer no immunity and give only partial relief lasting for a few hours. Many types or phases of allergic phenomena are not relieved by these compounds. In those manifestations where the drugs are effective, severe forms of the syndrome may be uninfluenced. The toxic symptoms in many cases prohibit the use of one drug or the other, and in many instances the discomfort of the side reactions exceeds those of the allergic complaint. It may well be that more prolonged and more extensive observation may disclose more profound or delayed toxic action of these drugs.

With the realization that we still do not possess the ideal antiallergic therapy, a number of pharmaceutical manufacturers are experimenting with new synthetic compounds. It is possible that these efforts will result in compounds having more perfect antihistaminic and antiallergic effects and less toxic action. Thus far the search for antiallergic drugs has been dependent on the finding of compounds having antihistaminic activity. Since it appears likely that the allergic reaction is not entirely dependent on the histamine response, it will be wise to include screening criteria other than histamine antagonism in a search for new antiallergic remedies. It is possible also that a search for a drug which will interfere with other phases of the antigen-antibody mechanism might yield more basic remedies.

S. M. F.

American Academy of Allergy

NEWS AND NOTES

Southwest Allergy Forum

The Southwest Allergy Forum will meet in Shreveport, Louisiana, on March 31 and April 1, 1947. Communications regarding the meeting should be addressed to Dr. Sim Hulsey, 505 Medical Arts Building, Fort Worth, Texas.

Southeastern Allergy Association

The Second Annual Meeting of the Southeastern Allergy Association will be held Jan. 18 and 19, 1947, at the Atlanta-Biltmore Hotel, Atlanta, Georgia. Hotel reservations should be made directly with the hotel. Dr. Katherine Baylis MacInnis, 1515 Bull Street, Columbia 49, South Carolina, is Secretary of the Association.

Appointment of Dr. Richard A. Kern

The appointment of Dr. Richard A. Kern as professor and head of the department of Medicine was announced on Sept. 26, 1946, by Dr. William N. Parkinson, Dean of the Temple University School of Medicine and Medical Director of the Temple University Hospital.

Dr. Kern, who succeeds Dr. Charles L. Brown, recently appointed Dean of the Hahnemann Medical School, comes to Temple from the University of Pennsylvania, where, since 1934, he has been professor of clinical medicine and chief of the outpatient department and the allergy section of the University Hospital.

A graduate of the University of Pennsylvania, first in 1910 when he was granted a Bachelor's Degree, then in 1914 as a Doctor of Medicine. Dr. Kern served in the Naval Reserve during both world wars. During the last war, where he held the rank of commodore, he was medical consultant for the entire South Pacific area. He was attached to the staff of Admiral Halsey.

On Feb. 2, 1942, the Naval Reserve Specialists' Unit at the University of Pennsylvania, which Dr. Kern formed in 1935, was called to active duty and dispatched to the hospital ship, "Solace," in the Pacific. In his last tour of duty for the Navy, Dr. Kern served as chief of medicine and of rehabilitation at the U. S. Naval Hospital in Philadelphia. He was separated from the Navy last March, after being on active duty for four years.

As a consultant to the Veterans' Administration, Dr. Kern is chief of its section for general medicine. He is associate editor of the American Journal of Medical Science, with which he has been connected since 1925. He is a Fellow of the American College of Physicians and holds membership in many national and local medical associations. He also belongs to Sigma Xi, Alpha Omega Alpha, Phi Gamma Delta, and Phi Chi.

Officers for 1947

To all Fellows of the American Academy of Allergy:

The Nominating Committee has completed its deliberation and reports the following slate of officers for 1947:

President—Dr. Will C. Spain
Vice-President—Dr. Karl D. Figley
Secretary—Dr. Theodore L. Squier
Treasurer—Dr. Leo H. Criep

Respectfully submitted

Dr. Harry L. Huber, Chairman
Dr. Louis Tuft
Dr. Robert Benson

This notification is in accordance with Article III, Section 3, of the Constitution of the American Academy of Allergy, which states that the report of the Nominating Committee shall be submitted in writing to the Fellows at least two months prior to the Annual Meeting.

Candidates for Fellowship and Membership in the Academy

To all Fellows of the American Academy of Allergy:

Below is a list of the candidates for elevation to Fellowship in the Academy, and the list of those applying for Membership in the Academy.

APPLICATIONS FOR FELLOWSHIP IN THE AMERICAN ACADEMY OF ALLERGY

Bernstein, Clarence, 740 North Magnolia, Orlando, Fla.
Bowen, Ralph, 3509 Montrose Blvd., Houston, Texas.
Brown, Ethan Allan, 75 Bay State Road, Boston, Mass.
Bubert, Howard M., Medical Arts Bldg., Cathedral and Read Streets, Baltimore 1, Md.
Dundy, Harold D., 1730 Carroll Street, Brooklyn 13, N. Y.
Friedlaender, Sidney, 18953 Appoline Street, Detroit 21, Mich.
Golan, Harry G., 104-35 Lefferts Blvd., Richmond Hill 19, N. Y.
Green, Mayer A., 6111 Jenkins Bldg., 500 Penn Ave., Pittsburgh 22, Pa.
Lieder, Louis E., 327 Osborn Bldg., Cleveland, Ohio.
Mosko, Milton M., 104 South Michigan Avenue, Chicago 3, Ill.
Perlman, Frank, 406 Medical-Dental Bldg., Portland 5, Ore.
Prigal, Samuel J., 55 Park Avenue, New York 16, N. Y.
Randolph, Theron, 700 North Michigan Avenue, Chicago 11, Ill.
Spielman, Aaron, 141 East 56th St., New York 22, N. Y.
Weitz, Myron A., 327 Osborn Bldg., Cleveland, Ohio.

APPLICATIONS FOR MEMBERSHIP IN THE AMERICAN ACADEMY OF ALLERGY

Aaronson, Abe L., 5532 Jackson Blvd., Chicago, Ill.
Abram, Lewis E., 10616 Euclid Avenue, Cleveland, Ohio.
Adams, Thomas J., 85-77 112th Street, Richmond Hill, N. Y.
Alexander, E. L., Suite 403, Medical Arts Building, Newport News, Va.
Altose, Richard Alexander, 233 Cobb Bldg., Seattle 1, Wash.
Armour, William S., 900 20th Street South, Birmingham 5, Ala.
Aronoff, Solomon, 6 No. Michigan Ave., Suite 1304, Chicago 2, Ill.
Bailey, A. L., 88 Chambers Street, Greenville, Pa.
Baird, K. A., 287 King St., West St. John, N. B., Canada.
Ballmer, Robert, Midland, Mich.
Banas, Charles F., 821 Cointon Street, Buffalo 10, N. Y.
Berke, Robert D., 3736 West 13th St., Chicago, Ill.
Blank, William Harvey, 909-910 Woodward Bldg., Birmingham 3, Ala.
Blue, Johnny A., 506 Hales Bldg., Oklahoma City, Okla.
Bukantz, Samuel C., Barnes Hospital, 600 So. Kingshighway, St. Louis 10, Mo.
Canseco, Carlos, Jr., Olivo 108, Col Aguila, Tampico, Tamps, Mexico.
Carliner, Paul E., 2217 South Road, Baltimore 9, Md.
Casper, Anne F., 25 Central Avenue, St. George, Staten Island, N. Y.
Catlin, R. C., 99 North Main Street, St. Albans, Vt.
Cenci, Vincent P., 50 Farmington Avenue, Hartford, Conn.
Chester, Saul W., 634 Broadway, Paterson 4, N. J.
Citron, A. Edward, 93 North Grand Avenue, Baldwin, N. Y.
Cleland, Charles E., 106 S. Fraley St., Kane, Pa.
Cohen, Stanley, 1441 Delachaise St., New Orleans, La.
Crowe, William R., 1107 Medical Arts Bldg., Atlanta, Ga.
Dees, Susan C., Duke University, Durham, N. C.
Dickstein, Bernard, 201 Dryden Bldg., Flint, Mich.

Douglas, C. L., 405 David Whitney Bldg., Detroit, Mich.
Dunn, Milton S., The Montefiore Hospital, 5th Ave. at Darragh, Pittsburgh 13, Pa.
Egbert, O. E., 1025 First National Bank Bldg., El Paso, Texas.
Ehrentheil, Otto F., 484 Commonwealth Ave., Boston, Mass.
Ehrlich, Norman James, 5009 Sheridan Road, Chicago 40, Ill.
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Annual Meeting of the Academy, Hotel Pennsylvania, New York City, Nov. 25, 26, and 27, 1946

PROGRAM

Monday, November 25

9:00 A.M.

"Bronchial Asthma in Patients Over 55 Years of Age. Its Cause and Control," Albert H. Rowe, M.D., Oakland, Calif. (12 minutes).

Discussion opened by Albert Vander Veer, M.D.

"Histamine Antagonists. VI. Comparative Antianaphylactic Activity of New Ethylenediamine Drugs in Guinea Pigs," A. R. Feinberg, M.D., S. Friedlaender, M.D., J. Rose, M.D., and S. M. Feinberg, M.D., Chicago, Ill. (12 minutes).

Discussion opened by Charles H. Eyermann, M.D.

"A Comparative Study: Pyribenzamine versus Specific Hyposensitization in the Treatment of Pollinosis," Carl E. Arbesman, M.D., Victor L. Cohen, M.D., and Howard Osgood, M.D., Buffalo, N. Y. (12 minutes).

Discussion opened by Robert Chobot, M.D.

"Group and Individual Psychotherapy as an Adjunct in the Diagnosis and Treatment of Allergy," Hyman Miller, M.D., and (by invitation) Dorothy W. Baruch, Ph.D., Beverly Hills, Calif. (15 minutes).

Discussion opened by John H. Mitchell, M.D.

"Localization—An Aid in the Causative Diagnosis of Contact Dermatitis. II. Dermatitis of the Hands," George L. Walbott, M.D., and (by invitation) John J. Shea, M.D., Detroit, Mich. (12 minutes).

Discussion opened by Abraham Walzer, M.D.

"The Electrocardiogastrographic Changes in Gastric Allergy," Jose M. Quintero, M.D., and (by invitation) J. Menendez Feros, M.D., Havana, Cuba (12 minutes).

Discussion opened by Louis Tuft, M.D.

"The Volumetric Incidence of Atmospheric Allergens. V. Spot Testing in the Evaluation of Species," Oren C. Durham, M.D., North Chicago, Ill. (10 minutes).

Discussion opened by Matthew Walzer, M.D.

12:30 P.M. Luncheon.

2:00 P.M.

"Studies on the Sensitization of Animals With Simple Chemical Allergens," W. Merrill Chase, Ph.D., Rockefeller Institute for Medical Research, New York (60 minutes).

"Evidence of Immunologic Specificity of Fraction 1 and Fraction 2 of Low Ragweed Pollen," William B. Sherman, M.D., and Arthur Stull, Ph.D., New York (12 minutes).

"The Immuno Chemistry of Ragweed Pollen. III. Studies on a Specific Skin-Reactive Fraction," Milton M. Mosko, M.D., and (by invitation) Kenneth C. Robbins, Ph.D., Chicago, Ill. (12 minutes).

"Chemical and Immunological Studies of Low Ragweed Pollen Extract," H. S. Baldwin, M.D. (by invitation), A. W. Moyer, M.D., P. F. De Gara, M.D. (by invitation, H. Brown, M.D., and K. J. Winfield, Jr., M.D., New York (20 minutes).

Discussion of this group of three papers will be opened by Robert A. Cooke, M.D.

Tuesday, November 26

9:00 A.M.

"Sulfadiazine Sensitivity. An Unusual Case With Successful Passive Transfer" (by invitation), Aubrey L. Whittemore, Jr., M.D., and P. F. de Gara, New York (10 minutes).

Discussion opened by Murray M. Albert, M.D.

"In Vitro Lysis of Sensitized Leucocytes by Specific Antigen," Theodore L. Squier, M.D., and Howard J. Lee, M.D., Milwaukee, Wis. (12 minutes).

Discussion opened by J. Warrick Thomas, M.D.

"Clinical Effects of Epinephrine by Inhalation. A Survey," Robert L. Benson, M.D., and (by invitation) Frank Perlman, M.D., Portland, Ore. (12 minutes).

Discussion opened by J. Harvey Black, M.D.

"Race and Sex as Factors in Reagin Formation" (by invitation), Eloise W. Kailin, M.D., Alexander G. Davidson, and Matthew Walzer, M.D., Brooklyn, N. Y. (12 minutes).

Discussion opened by Leon Unger, M.D.

Business Meeting.

12:30 P.M. Luncheon.

2:00 P.M.

"Allergic States and Pathologically Similar Conditions. Pathologic Differential Diagnosis," Milton G. Bohrod, M.D., Pathologist, Rochester General Hospital, Rochester, N. Y. (60 minutes).

"Skin Tests in Dogs With Common Allergens," Jose Cortes, M.D., Mexico City, Matthew Brunner, M.D., and (by invitation) Irving Altman, D.V.M., Brooklyn, N. Y. (12 minutes).

Discussion opened by Milton B. Cohen, M.D.

"Measurements of Vital Capacity in Asthmatic Subjects Receiving Histamine and Acetyl-beta-methyl-choline" (by invitation), John J. Curry, M.D., and Francis C. Lowell, M.D., Boston, Mass. (12 minutes).

Discussion opened by Richard A. Kern, M.D.

"Correlation Between Symptoms of Hay Fever and Titer of Thermostable Antibody," Harry L. Alexander, M.D., and (by invitation) Mary B. Johnson, M.S., St. Louis, Mo. (12 minutes).

Discussion opened by Mary H. Loveless, M.D.

"Study of the Effect of Radon on Children With Asthma" (by invitation), Dean A. Moffatt, M.D., Arthur T. Ward, M.D., Samuel Livingston, M.D., G. Frederick Hieber, M.D., and Leslie N. Gay, M.D., Baltimore, Md. (12 minutes).

"Pollen Tolerance—Its Bearing on the Treatment of Hay Fever," Francis M. Rackemann, M.D., Boston, Mass. (12 minutes).

Discussion opened by Walter S. Burrage, M.D.

Annual Dinner.

President's Address—"A New Viewpoint on Allergy," Stearns S. Bullen.

Wednesday, November 27

9:00 A.M.

"The Use of a Simple Container for the More Efficient Defatting, Drying, Storage, and Extraction of Pollens" (by invitation), Margaret B. Strauss, M.S., and Will C. Spain, M.D., New York (10 minutes).

"Difference in Properties of Wheals Produced by Electrophoresis and by the Intracutaneous Technique" (by invitation), Eugene Walzer, M.D., Jerome Sherman, M.D., Katherine Bowman, A.B., and Matthew Walzer, M.D., Brooklyn, N. Y. (12 minutes).

Discussion opened by Oscar Swineford, Jr., M.D.

Symposium on Eczema-Dermatitis.

A. "Contact Type Eczematous Dermatitis; Modern Classifications and Remarks on Therapy," Marion B. Sulzberger, M.D., New York (60 minutes).

B. "Infantile Eczema. Newer Concepts of Classification, Pathogenesis and Management," Lewis Webb Hill, M.D., Boston, Mass.

C. "Atopic Dermatitis in Infants, Children and Adults With Special Reference to the Role of Inhalents and Dander," Frank A. Simon, M.D., Louisville, Ky.

D. "Occupational Dermatitis With Special Reference to Eczema-Dermatitis of the Hands," Stephan Epstein, M.D., Marshfield, Wis.

"Charcot-Leyden Crystals. A Study of the Conditions Necessary for Their Formation" (by invitation), Max Samter, M.D., Chicago, Ill. (12 minutes).

Discussion opened by Wyndham B. Blanton, M.D.

"Penicillin Aerosol in the Treatment of Respiratory Infections in Allergic Individuals," Samuel J. Prigal, M.D. (by invitation), Lawrence J. Morganbesser, M.D., and Frederick P. McIntyre, M.D. (12 minutes).

Discussion opened by Leo H. Criep, M.D.

The following papers will be read if time permits.

"Immunologic Studies in Patient Sensitive to Heparin," Max Grolnick, M.D.

"Severe Allergic Reactions During Cystoscopy. Report of a Near Fatality Due to Proved Sensitization to Material (Caroid Solution) Injected into the Kidney Pelvis," Henry D. Ogden, M.D., Harry L. Zengel, Jr., M.D., and John F. Lally, M.D.

"Benign Paroxysmal Peritonitis. II. Further Observations," Sheppard Siegal, M.D.

"A Critical Evaluation of Some Ideas and Procedures in Allergy," Marion C. Davidson, M.D.

"Psychosomatic Rhinorrhea and Psychosomatic Dyspnea," Louis Sternberg, M.D.

"Carotid Sinus Sensitivity With Clinical Epileptic-like Seizures, Relieved With the Development of an Acute Thyrotoxicosis, Treated With Thiouracil and Iodine, Followed by Sub-total Thyroidectomy," Ralph H. Spangler, M.D.

"The Assay of Ragweed Pollen Extract by Means of the 'Quantal' Response," Elmer L. Becker, M.D.

"Personality Factors in Vaso-Motor Rhinitis," John H. Mitchell, M.D., Charles A. Curra, M.D., and Ruth N. Myers, B.S.

"An Unusual Case of Photo-Sensitivity," G. Frederick Hieber, M.D., Dean A. Moffat, M.D., and Leslie N. Gay, M.D.

"Quantitative Micro Methods in the Study of Precipitation of Rabbit Antiragweed Serum by Ragweed Pollen Extracts and the Measurement of 'Blocking' Antibody," Samuel Buckantz, M.D., and Mary B. Johnson, M.S.

Book Reviews

Allergy. Erich Urbach, M.D., and Phillip M. Gottlieb, M.D., Second Edition, New York, 1946, Gruene and Stratton, pp. 968, illustrated.

This is probably the most complete reference book on allergy ever published. It is beautifully printed with abundant, clear illustrations, and documented with over 3,300 references. That is the value of the book, for here one may find a descriptive bibliography on almost any phase of the subject. Exception is taken here, as formerly, with several of the authors' interpretations, such as their group classification of allergic, hetero-allergic, and nonallergic pathergy and subgroups parallergy, metallergy, etc. It all seems so involved. And here the authors' propeptan therapy, discarded by most American allergists as worthless, still is advocated. If the reader desires an over-all work of reference, this book is well worth possessing.

Allergy in Practice. Samuel M. Feinberg, M.D., ed. 2, revised, Chicago, 1946, Year Book Publishers.

When the first edition of this book was published, it was considered a good text on conventional phases of allergy with emphasis on mold allergy, in which the author is so interested. The broader aspects of allergy which are engaging the attention, not of allergists, but of pathologists, immunologists, and many clinicians, received scant attention.

It is a matter of gratification, therefore, to find discussion in this second edition of vascular allergies and their suggestive relationship to the disseminated lupus erythematosis group, and tropical eosinophilia, as well as a chapter on histamine in anaphylaxis and allergy by Dr. Carl Dragstedt. Following this is a timely chapter on histamine antagonists. These inclusions identify this treatise on allergy as up to date and a valuable book to possess.

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